Clinical and laboratory investigation into heroin and opioid overdose risk

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Clinical and Laboratory Investigation into Heroin and Opioid Overdose Risk

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Abstract

Background: Globally, more than 100,000 people die annually from opioid overdose, and this number continues to increase. In the UK, opioid-related deaths are at an all-time high. The depressant effects of opioids on breathing centres in the brain cause 'respiratory depression' with effects on regular breathing rhythm and neural respiratory drive (signals coming from brain to breathing muscles), which then impairs the adequately balanced levels of blood oxygen and carbon dioxide. Mechanisms of opioid overdose and the degree of opioid-induced respiratory depression among long-term users are not well understood.

Aims: This thesis incorporates retrospective analyses as well as direct clinical investigations to examine risk factors for overdose, as captured through clinical samples and in a clinical research facility, exploring influence of dose, route of administration and pre-existing disease.

Methods: Primary and secondary data were collected and analysed. Primary data collection involved two clinical studies utilising novel objective markers of respiratory depression. First, an observational study investigated the severity of respiratory depression in long-term heroin users on an opioid substitution treatment. The second clinical study, in a clinical research facility, examined effects of varying doses of pharmaceutical heroin (diamorphine) on physiological markers of respiratory depression and observed and subjective ratings of drug effect. Secondary data analysis involved physiological data from a previous clinical study, and data extraction from historical literature.

Results: Major impairment of respiratory function was identified across a broad clinical sample of dependent opioid users, and particularly following intravenous heroin administration (studied in an experimental clinical laboratory context).

Conclusions: Without a practical, 'gold standard' measure of respiratory depression, it is crucial that reliable and sensitive techniques are used to elucidate the complex physiological responses to opioid use. Important next steps are identified for research to inform better understanding and better public response to the opioid overdose crisis.

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Abbreviations

Abbreviation	Meaning
A/C	Alternating Current
A/D conversion	Analog-to-Digital conversion
AIDS	Acquired Immunodeficiency Syndrome
BBB	Blood Brain Barrier
BMI	Body Mass Index
CDC	Center for Disease Control
COPD	Chronic Obstructive Pulmonary Disease
DRD	Drug-Related Death
DRG	Dorsal Respiratory Group
ECG	Electrocardiogram
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EMG	Electromyogram
EMG_{para}	Parasternal Intercostal Electromyogram
EMG_{para}%max	EMG_{para} as a percentage of maximum
ETCO2	End-Tidal Carbon Dioxide
FEV_1	Forced expiratory volume in one second
fMRI	Functional Magnetic Resonance Imaging
FRC	Functional Residual Capacity
FVC	Forced vital capacity
GCS	Glasgow Coma Scale
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IH	Inhalation
IM	Intramuscular
IQR	Interquartile Range
IV	Intravenous
log	Logarithm
µV	Microvolt
MST	Morphine Sulphate
NIDA	National Institute on Drug Abuse
NRD	Neural Respiratory Drive
NRDI	Neural Respiratory Drive Index
NRS	Nationals Records of Scotland
ONS	Office for National Statistics
PEEP	Positive End Expiratory Pressure
pCO_2	Partial Pressure of Carbon Dioxide
pO_2	Partial pressure of oxygen
RMS	Root Mean Square
SD	Standard Deviation
SLaM	South London and Maudsley NHS Foundation Trust
SpO_2	Pulse Oximetry
$TcCO_2$	Transcutaneous Carbon Dioxide
TLC	Total Lung Capacity
UNODC	United Nations Office on Drugs and Crime
V_E	Minute Ventilation
Vf	Respiratory Rate
Vi	Mean Inspiratory Flow
VT	Tidal Volume
WHO	World Health Organisation

Aims of the Thesis

The underlying basis of opioid overdose is alterations at the respiratory centres in the brain caused by inhibitory effects of opioid agonists, leading to respiratory depression. Immediately after injection of heroin, a decrease in respiratory drive can occur, leading to hypoventilation, resulting in an increase in carbon dioxide (hypercapnia) and a reduction in blood oxygen levels (hypoxaemia). This is presumed to underlie fatal opioid overdose cases. Even whilst patients are tolerant, experienced and administer stable doses of pharmaceutical opiates that are individually-titrated, overdose can still occur. Inter-subject variability and the factors underlying this susceptibility to overdose in certain individuals are poorly understood.

This thesis aims to:

1. investigate the prevalence and severity of opioid-induced respiratory depression in long-term opioid-dependent users;
2. examine the influence of personal drug use and addiction treatment characteristics on the severity of respiratory depression;
3. investigate the relevance of underlying respiratory disease in opioid-dependent users;
4. examine the influence of route of heroin administration on respiratory depressant responses to a dose of injectable heroin;
5. investigate physiological responses to varied doses of injectable heroin as a marker for overdose;
6. investigate subjective and observed ratings of drug effect in response to heroin dose and variations of heroin dose.

Chapters 1 and 3 are descriptions of literature and provide rationale behind the aims of this thesis. Chapter 2 examines historical data on deaths from a particularly distinct time in UK heroin addiction treatment. The main results for the thesis begin in chapter 5 which is devoted to an observational study of respiratory function and respiratory depression among opioid users compared to non-addict controls. It aims to investigate a variety of characteristics and factors thought to underlie overdose. Chapter 6 incorporates secondary analysis of a previous study of acute heroin administration and explores the effect of differing routes of injecting.

Chapter 7 discusses the development of the heroin overdose study (AOO). Through service user consultations, key aspects of the study design are described. The many obstacles and difficulties of conducting experimental clinical trials are also highlighted in this chapter. Chapter 8 is the final results chapter of this thesis and details the results of this dose-incremental, single-blind trial using physiological and psychological measures to examine dose changes.

1 Overdose, a Global Overview

1.1 Preface

Heroin-related mortality has been, and is still, a major public health concern in the UK and globally (Office for National Statistics (ONS), 2018; United Nations Office on Drugs and Crime (UNODC), 2018; World Health Organisation (WHO), 2017). There have been increases in heroin- and opioid-related deaths across the globe. Since 2014, there has been a staggering 64% increase in opioid-related deaths in England and Wales, and rates are now at the highest since records began (ONS, 2018). The latest figures show that the number of deaths is relatively similar to the previous two years, indicating that it might have stabilised.

In 2006, half of all reported heroin-related deaths in Europe were from the UK and Germany (Frisher et al., 2012), and this still continues to be the case with the UK taking up 31% and Germany around 15% (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2017). This has attracted surprise as well as concern as the number of injecting drug users appeared to be decreasing in the UK, Europe and much of the world (EMCDDA, 2012; Hay et al., 2012; UNODC, 2014). In fact, in the UK, the prevalence of heroin use has consistently been the lowest of all commonly used drugs (Home Office, 2012), yet opiates are most significantly and disproportionately involved in drug-related deaths (ONS, 2016).

With a large focus on overdose deaths specifically, this opening chapter draws attention to the national and global overview of the opioid crisis and concludes on the reason for the crisis in the UK over the last five years, with a discussion of the problems faced in analysing drug-related deaths data.

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1.2 Overview of the Prevalence of Drug Use, Morbidity and Mortality

In 2015, 5% of the global adult population used drugs at least once, and of those users, 0.6% had a drug use disorder (UNODC, 2018). The burden of disease is usually calculated as disability-adjusted life years (DALYs) (UNODC, 2017). In 2015, opioids accounted for the largest proportion of burden of disease attributable to drug use disorders with 70%, or almost 12 million DALYs (UNODC, 2017). A review of literature found that 3% of patients taking opioids for chronic non-cancer pain developed opioid use disorders (Fishbain, Cole, Lewis, Rosomoff, & Rosomoff, 2008).

It is thought that around 35 million people worldwide (range 28.3 million to 42.7 million) misuse prescription opioids and 17.7 million are estimated to have used the opiates heroin and opium (UNODC, 2017). This is a growing concern in the USA where it has been coupled with an increase in the use of heroin and fentanyl, which has led to an epidemic and increase in morbidity and mortality related to opioids. According to the UNODC world drug report, there are also indications that heroin use in Western and Central Europe is increasing, indicating that the long-term downward trend of heroin use might be coming to an end (UNODC, 2017).

Additionally, in some countries, such as Estonia and Finland, a combination of a reduction of heroin availability and an increase in substitution treatment for heroin use disorders has meant that transitions to other opioids such as fentanyl have been observed. The heroin market plummeted in 2001 and 2002 and was displaced by fentanyl and buprenorphine. In a study in 2014, 18 European countries reported that more than 10% of opioid treatment admissions were for opioids other than heroin (including diverted methadone, buprenorphine, fentanyl, codeine, morphine, tramadol and oxycodone) (EMCDDA, 2016). Acetylfentanyl, an analogue of fentanyl, is also a growing concern, with 32 reported deaths in Europe between 2013 and 2015, two of which were in the UK (UNODC, 2017).

A study into the prevalence of non-medical use of opioids was conducted through parallel surveys in Denmark, Germany, Spain, Sweden and the UK in 2014 (Novak et al., 2016). Spain, followed by the UK, reported the highest prevalence of non-medical use of opioids for both lifetime and past-year use. Higher levels of prescription opioid misuse were seen in older age groups and the unemployed (Novak et al., 2016).

1.3 Global Drug-Related Deaths

There are many different definitions of 'drug-related deaths', but they include all or some of the following: overdoses, deaths from Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) and Hepatitis C Virus (HCV) through injecting drugs; behavioural disorders by use of psychoactive substances; intentional self-harm and self-poisoning (suicide) by exposure to psychotropic substances; unintentional deaths and trauma resulting from drug use (e.g. motor vehicle accidents) (UNODC, 2017).

Globally, it is estimated that there were 450,000 deaths attributable to drug use in 2015 (WHO, 2017). Of these, just over one-third (167,750 deaths) were the direct result of drug use (76% of which were related to opioids), and two-thirds were indirectly attributable to drug use e.g. from HIV/AIDS and HCV contracted through unsafe injecting practices (UNODC, 2018). The Global Burden of Disease study of 2015 stated that most of the causes of morbidity and mortality could be attributed to drug use (Kassebaum et al., 2016). North America sees the highest number of drug-related mortality, with one in four deaths occurring here. Australia and New Zealand (Oceania) also see a high drug-related mortality rate, at 2.5 times the global average (UNODC, 2017).

1.3.1 North America

Overdose deaths continue to rise, and have tripled between 1999 and 2015 and increased by 11.4% in the past year alone to the highest level ever recorded in the USA (Rudd, Seth, David, & Scholl, 2016). Between 2012 and 2015, the number of overdose deaths from synthetic opioids other than methadone increased by 265% (and between 2014 and 2015 by 72%) and was thought to be driven by illicit fentanyl use. In 2016, 948,000 people aged 12 and older used heroin and 12 million people misused prescription opioids (Substance Abuse and Mental Health Services Administration (SAMHSA), 2017). In the same year, 63,632 total drug overdose deaths were observed, 66% of which were from opioids (CDC, 2017). In the USA, it is estimated that nearly 40% of heroin-related deaths involved fentanyl, and in studies examining non-fatal cases, many users had been unaware that fentanyl was what they had consumed (Frank & Pollack, 2010). According the most recent figures, in New York City, fentanyl was the most common substance involved across all overdose deaths (57% of deaths) in 2017 (NYC Department of Health and Mental Hygiene, 2018). Fentanyl is also sold as 'ecstasy' or as counterfeit versions of OxyContin®, alprazolam and hydrocodone, among others (see section on Pharmaceutical Opioids for further detail on this). In relation to heroin, the increases in overdose deaths were 119% between 2012 and 2015, 23% between 2014 and 2015 and 21% between 2015 and 2016 (CDC, 2017). Overdose deaths from prescription opioids (other than methadone) have stabilised over the last four years, although they are still at a very high level (CDC, 2015; Compton, Jones, & Baldwin, 2016). This is thought to be driven by the prescription monitoring programme and prescribing guidelines.

In Canada, British Columbia has seen the highest overdose death rate at 285 per million population aged 15-64 years. This is in fact higher than the rate seen in the USA (246 per million). This represents a 79% increase from 2015 and a 240% increase from 2012. Similarly, fentanyl accounts for a large proportion of these deaths (British Columbia Centre for Disease Control (BCCDC), 2017).

1.3.2 Europe

Overall in Europe, opioid users are five to 10 times more likely to die than people of the same age and gender who do not use opioids (EMCDDA, 2017). Cohort studies of high risk drug users show mortality rates to be around 1 to 2% per year (EMCDDA, 2017). Other causes of death indirectly related to drug use (infections, accidents, violence and suicide) are also important. The EMCDDA states that chronic, pulmonary and liver conditions commonly occur in this population and also account for some of the increase in deaths amongst older and chronic drug users (EMCDDA, 2017).

Mortality rate due to overdose in Europe is 20.3 deaths per million, and there is a large discrepancy between males and females, with 32.3 deaths, and 8.4 deaths per million seen, respectively (EMCDDA, 2017). With regards to age, the peak age group for males is 35-39, and for females it is 30-34. Mean age is actually lower in males at 38, compared to 41 years for females. The situation in Northern Europe is considerably more severe; eight northern

European countries reported rates of over 40 deaths per million, with the highest being reported in Estonia (103 per million), Sweden (100 per million), Norway (76 per million) and Ireland (71 per million) (UNODC, 2017).

Three-quarters (78%) of people dying from overdose in Europe are male. However, caution should be taken when interpreting some of the data because of issues such as underreporting and reporting delays in coroners' reports and death registration. The mortality rates should be considered as 'provisional minimum values' (EMCDDA, 2017).

The UK accounts for the largest proportion (36%) of the total number of overdose deaths in Europe (EMCDDA, 2016). The combined impact of mortality rates that Germany and the UK have in Europe is partly related to the size of the population and also due to underreporting in other countries. In addition to the UK, increases in overdose deaths are being reported in Spain, Lithuania, as well as Germany and the Netherlands. Turkey is also reporting increases but this is thought to be due to improved methods in data collection and reporting (EMCDDA, 2017).

1.3.3 United Kingdom

In England and Wales, the number of deaths involving heroin and/or morphine more than doubled between 2012 and 2017 and have been at the highest on record since 2016 (Figure 1-1) (ONS, 2018). Over half (53%) of all deaths related to drug poisoning in 2017 involved an opiate (mainly heroin and/or morphine where there were 1,164 cases) (ONS, 2018). Deaths involving heroin and/or morphine remained relatively stable between 2016 and 2018, with only slight fluctuations (ONS, 2018). The latest figures appear to show a slight decrease by 45 cases which is the first decrease since 2012, and is related to the decrease seen in the number of male drug misuse deaths (ONS, 2018). However, female deaths have increased year on year and is also the highest level reported since records began. Mortality rates for heroin/morphine were 33.1 deaths per 1 million population for males and 9.5 deaths per 1 million for females, and the greatest increase was seen in the 40-49 age group, which is now the group with the highest level of mortality. Previous years saw the 30-39 age group having the highest levels (ONS, 2018).

Deaths involving heroin/morphine had declined between 2008 and 2012, with a particularly sharp fall between 2009 and 2011. The recent reversal means the mortality rate in 2015 and 2017 was the highest since records began in 1993 and now exceeds the previous peak in 2008, which occurred before the 'Heroin Drought' (see following section). The number of reported deaths involving heroin/morphine is actually likely to be an underestimate, as some coroners simply record 'opiate overdose' on the death certificate and do not specify which opiate drug was involved (ONS, 2016).

Additionally, National Records of Scotland (NRS) data show that Scotland has seen an increase of 23% from 2015 to 2017, which is now the highest since comparable records began in 1996 (NRS (National Records of Scotland), 2018). Opioids contributed to 88% of these deaths with methadone deaths also at a peak (42% of all drug-related deaths) (NRS (National Records of Scotland), 2018). In Northern Ireland, although figures are small, creating difficulty in comparison with the rest of the UK, increases in drug-related deaths have also been observed (ACMD, 2016). It has been reported that there was an increase by almost three times between 2000 and 2013 (NISRA, 2016) and there appears to be particular concern about prescription drugs (BBC, 2017).

1.4 Why Has There Been a Recent Increase in Overdose Deaths in England and Wales?

There are many factors that have been suggested to be responsible for the recent increase in overdose deaths observed in England and Wales. Reports related to this rise in deaths state that they have been mostly driven by increases in heroin purity and availability, as well as an ageing cohort of heroin users who have a range of medical conditions attributed to long-term drug use. Purity as a pharmacological risk factor for overdose is analysed more extensively from the pharmacological perspective in chapter 3. This chapter focusses on the illicit drug market, and purity fluctuations therein, as the reason for the increase in deaths. The 2016 ONS report on drug-related deaths had the most detailed explanations for these increasing trends (ONS, 2016). These were centred on purity and the 'Heroin Drought' of 2010/11.

1.4.1 Heroin Drought and Purity Changes

Heroin droughts/shortages have occurred at various time points around the world (e.g. in Australia and Canada in 2001). In the UK, when a surge of drug-related deaths was first reported in the ONS report of 2014, it was suggested that the increase in heroin-related deaths may have been as a result of a 5% to 10% increase in the purity of street heroin. The report stated:

> This increase in street purity after a time of lower purity may partly or wholly explain the increase in heroin related deaths in 2013, as users may have had reduced tolerance to the drug. (ONS, 2014)

Subsequently, in relation to the 2015 data, the ONS stated:

> The heroin drought affected the purity of "street" heroin, which fell from 46% in September 2009 to 17% in mid-2012, but then increased again in each of the last 3 years reaching an average of 44% in 2015 (ONS, 2016 based on Serious Organised Crime Agency (SOCA), 2011).

However, there is currently not enough of a consistent relationship between purity and overdose in fatal toxicological reports. Deaths occur most commonly in people in their 30s and 40s, who are dependent, tolerant, long-term injecting users, and thus, purity variations would not greatly impact this group of people (Bauer et al., 2008; Bird, Hutchinson, Bird, & Hutchinson, 2010; Darke, 2011b; Darke & Farrell, 2014; Darke, Mills, Ross, & Teesson, 2011;

Degenhardt et al., 2011; Stenbacka, Leifman, & Romelsjo, 2010). Detailed discussion of purity and its relation to risk of overdose death is discussed in chapter 3.

A previous explanation by the ONS has suggested that there is sufficient evidence to state that overdoses are associated with higher drug purity, citing a cross-sectional study on non-fatal overdose deaths in Malaysia (Bazazi et al., 2015). While this paper relays an important finding on the high prevalence of non-fatal overdoses amongst injecting drug users, the study does not compare different purities of heroin, thus it is inappropriate to draw parallels to purity and overdose deaths. The ONS also concluded that the increase in user-level purity, and the changes in price, may partly explain the increase in heroin-related deaths since 2012 (ONS, 2016). However, it would seem that data on purity appear more fluid and fluctuating than is suggested by the ONS.

The Serious Organised Crime Agency's (SOCA; now replaced by the National Crime Agency (NCA)) used to report on the national purity data from seizures from import to street level in their annual reports. Their report of 2014, from which these references to purity are made, states:

> Purity levels of heroin detected at the UK border remained at around 50%, while purity at street dealer level remained at around 25% (SOCA, 2014).

Further, focusing on the SOCA figures for 2009 to 2013, the period of time in which the 'Heroin Drought' had occurred, firstly, there is a clear sign that the 'Heroin Drought' was a real phenomenon, with 'street' purities dropping from a reported 46% in 2009/10 to 19% in 2011/12. It appears that the levels only began to re-stabilise a couple of years after this period, with SOCA stating in 2012/13 that "at street dealer level the purity of heroin was mostly between 15 and 20%" (SOCA, 2014). The report suggests that purity levels had slowly been recovering from the teens to low twenties to around 25% in 2014, rather than the jump suggested by the ONS report (ONS, 2016).

Eurofins Forensic Services (formerly LGC Forensic Group) is a national laboratory that runs drug-testing services on seizures from law enforcement agencies in England and Wales. During the same time period, January to March 2013, the reported overall average heroin purity was 27%, with small (less than 0.3g) 'street' deals averaging 29%. After this time, the availability of purity data becomes sparser and much of the existent data on purity since this time have not been publicly available. Fortunately, I have been given permission from Eurofins Forensic Services to incorporate purity data over a 10-year period into this thesis (Eurofins, 2018) (Figure 1-2). The data exist as percent purity every quarter and are compiled from various locations in England and Wales and from over 2,000 samples per quarter (Eurofins, 2018). While it is not possible to differentiate between street and import level from the data, it provides an overarching picture of the fluctuations that have been seen during this 10-year period. As stated previously, these data also support the abovementioned purity levels. There was a peak purity level of 44% in the second quarter of 2015, which was reached after a steady rise from the nadir of 16% observed during the drought between 2010 and 2011. Across the same time periods (until 2015), increases in heroin/morphine-related deaths were being observed year on year in England and Wales. It has since stabilised (ONS, 2018). This suggests that perhaps purity levels are more fluid and fluctuating than has been previously acknowledged, and that the 'recovery' from the drought was more of a gradual process that is unlikely to have had a big impact on the experiences of regular users.

There are, however, some limitations to these purity data from Eurofins. As stated earlier, it is not possible to differentiate between street and import level samples from the data that were received. Additionally, these data are averages for each quarter, and it has not been possible to obtain ranges or standard errors for each data point. Eurofins also compile data from contracted regions of the country, which has a twofold impact: 1) it does not cover every region of England and Wales (and none of the rest of the UK); and 2) contracts can stop and start and thus, some regions have not been consistent throughout this time period. It is also uncertain whether the date stated is the date of seizure or the date of receipt of the sample. Nevertheless, these are very important data and there are a great number of samples to draw from. It would be of huge interest to examine these data in more detail but that is beyond the scope of this thesis.

Interestingly, an additional finding from the Eurofins purity data is that a second sharp decrease in purity was seen in between the fourth quarter of 2016 and first quarter of 2017. This drop was by 10% (from 39% to 29%) and subsequently rose back to original purity levels of 44% after three further quarters in 2017 (with a 5% rise in the subsequent quarter). This has not been publicly documented, and thus, there is no discussion of it in the literature. A change of 10% is perhaps not a considerable one, however, the fluctuations observed during the 'Heroin Drought' of 2010/2011 instigated an explanation based on rises of, at most 5% and at least 1% per quarter, and thus, it does appear that more attention should have been given to this 'drought' of 2016/2017.

1.4.2 Gender

The increases in deaths have affected both genders with a sharper increase being observed amongst males, and a steady increase or stable rate being seen amongst females for the last two decades. In fact, female opioid-related mortality has seen a steady increase in recent years; the latest figures show a 12% increase from the previous year in heroin/morphine deaths specifically for females (ONS, 2017). This covers the period of the 'Heroin Drought' (M. Harris, Forseth, & Rhodes, 2015), where a purity decrease was seen, and therefore, somewhat contradicts the explanation that a 5% to 10% increase in purity played a role in the rising number of deaths.

In order to address the issue, the ONS states that the reason for the differences between genders is due to the fact that female deaths are more likely to be suicides rather than accidental overdoses, which are less likely to be impacted by the changes in purity. They state in their 2016 report:

> A more detailed analysis of the data suggests that a greater proportion of female deaths included in this section involve morphine rather than heroin – less than 40% of female heroin/morphine deaths actually mention heroin on the death certificate compared with more than 60% of male deaths. This means that female deaths are less likely to be affected by changes in the heroin market in England and Wales. (ONS, 2016)

Much of the focus on fluctuations and increases of drug-related deaths has been on male deaths, primarily because these are much higher and presumed to be more influenced by changes in the illicit drug market. Whilst some argue that female deaths have a different profile (e.g. greater number of suicides and greater use of pharmaceutical drugs), very little investigation has actually been conducted into this.

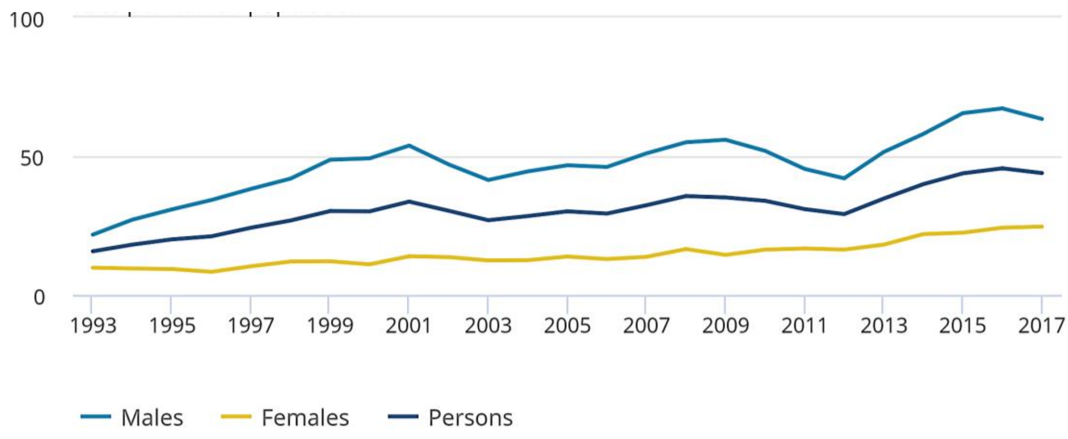

Figure 1-1: Graph of year-on-year drug-related deaths broken down by gender from 1993 to 2017 (ONS, 2018).

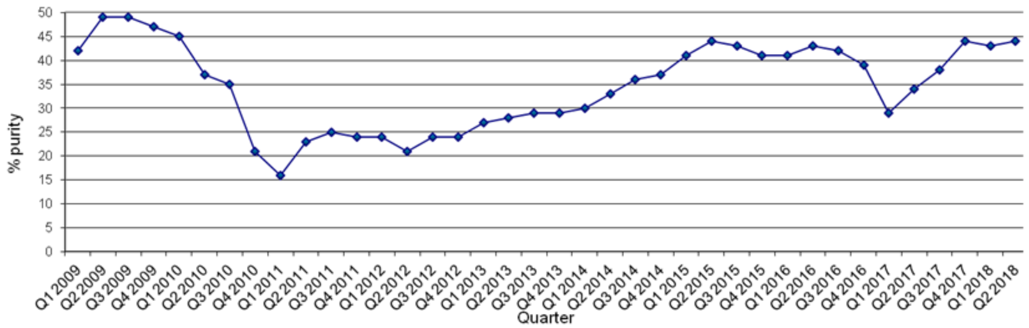

Figure 1-2: Quarterly average purity data for heroin, 2009-2018. Reproduced with permission from Eurofins Forensic Services, Class A Bulletin, 2018 (Eurofins, 2018).

1.5 The Issue of Prescription Opioids

Non-medical use of drugs is defined as 'using medications that were not prescribed for a patient or were taken only for the experience or feeling that they caused' (Lipari & Hughes, 2017). Use of pharmaceutical opioids is involved in acute and chronic pain management, for the treatment of opioid use disorders, as well post-surgical care, and palliative therapy. Prescription opioids, pharmaceutical opioids and synthetic opioids are usually referred to interchangeably. These include drugs such as oxycodone, hydrocodone, hydromorphone, fentanyl, as well as methadone and buprenorphine.

Interestingly, in the last year in Europe, methadone deaths exceeded heroin-related deaths in Croatia, Denmark, France and Ireland (UNODC, 2017). In the UK, fentanyl deaths rose by 29% between 2016 and 2017 (ONS, 2018). It is thought that the cause of these increases is related to the issue of legal alternatives to heroin (Griffiths et al., 2014). Australia has also seen a high level of prescription opioid use. However, it is impossible to discuss prescription opioid use and mortality without focussing on the USA which has dominated the discussion on this topic.

1.5.1 Prescription Opioid Use in the USA

Hospital emergency visits involving the misuse of prescription opioids have increased by 153% between 2004 and 2011 (Center for Behavioral Health Statistics and Quality, 2013). The number of admissions to treatment clinics linked to opioids has also seen a four-fold increase between 2002 and 2012 (SAMHSA, 2014). Rates of death increased four-fold between 2000 and 2014 due to prescription opioid overdose. Although a reduction was seen in 2012 and 2013 from 2011's peak, the 2014 data shows an all-time peak, greater than previous records (Figure 1-3). It is thought that the policies that are used to reduce the prescription opioid epidemic are causing some of these increases in mortality rates. There was a 145% increase in heroin use in from 2007 to 2014, and mortality from heroin overdose more than quintupled from 2000 to 2014 (SAMHSA, 2016).

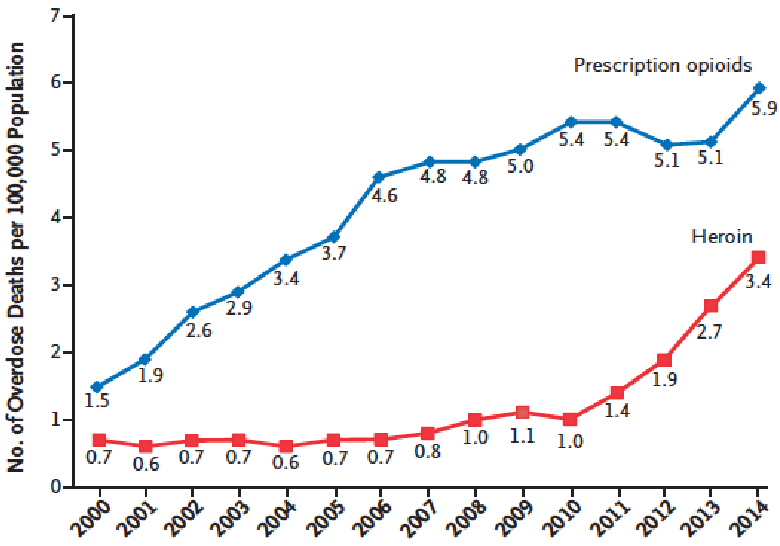

Figure 1-3: Age-adjusted rates of deaths in relation to prescription opioids and heroin in the USA, 2000-2014 (CDC, 2015).

1.5.2 Causes of Prescription Opioid Misuse and Mortality

Different driving forces are thought to play a role in high levels of prescription opioid misuse around the world. High level of misuse of prescription opioids (not including methadone) have been seen in the USA and Australia where opioids are fairly easy to access, however, having easy access to opioids does not always lead to their misuse or addiction. In some cases, even the opposite is true, where there is restricted access to opioid painkillers, but high levels of misuse of these substances (Degenhardt et al., 2007; Fischer, Gooch, Goldman, Kurdyak, & Rehm, 2014).

In the USA the issue of prescription opioid misuse is thought to be primarily shaped by the health system. The misuse of prescription opioids in the USA has been on the increase since 1997 by the medical practice of prescribing more and higher doses of opioids (King, Fraser, Boikos, Richardson, & Harper, 2014). From 2007 an increase in heroin was also observed and was attributed to the availability of pure and cheaper heroin on the market (Hughes et al., 2016). This is somewhat different to the arguments provided in the UK; heroin was not a new drug in the UK, and the claims were made around a sudden increase in purity after a drought where lower quantities of heroin were available, as mentioned previously. In the USA, it has been seen that a $100 decrease in the price per pure gram of heroin resulted in 2.9% increase in the number of hospitalisations for heroin overdose (Unick, Rosenblum, Mars, & Ciccarone, 2014). Also, current heroin users are more likely to have used prescription opioids and then switched to heroin use (Kolodny et al., 2015; UNODC, 2017). Overall, the evidence seems to suggest that the non-medical use of prescription opioids is not related to the initiation of heroin use and other factors have contributed to the increase in heroin use and related mortality (Compton et al., 2016).

1.6 Problems with Interpreting Global Drug-Related Deaths Data

The difficulties of studying overdose are substantial. It is difficult to conduct controlled trials on overdose as they are usually either observational or post-mortem (Frisher et al., 2012), with some exceptions including the N-ALIVE trial of take-home naloxone provision, post-prison release. Furthermore, it is also difficult to compare studies of differing drug use patterns and responses to overdose which vary from country to country. Cultural and legal factors influencing the study, populations and outcomes may also play a role here. In terms of recording deaths, general mortality registries do not always accurately represent deaths with an 'unknown' or insufficiently specified cause, which might actually be overdoses (EMCDDA, 2009).

Furthermore, importantly, it is reported that many countries actually underestimate the drug-related death rates (Buchanich, Balmert, Williams, & Burke, 2018; Goldberger, Maxwell, Campbell, & Wilford, 2013; ONS, 2018). In some reports, statistical coding excludes those deaths where a specific drug is not reported, rather it is focussed solely on coding relating to 'opioid-related' deaths. In the USA, one analysis indicates that more than 70,000 unspecific, unintentional overdose deaths (over a 17 year period) could be opioid-related (Buchanich et al., 2018).

Thus, any comparisons between countries should be made with caution due to the differences in reporting methods (UNODC, 2017). Even within the UK, there are issues with the comparison of trends between England/Wales and Scotland which have differing definitions and methods of registration (Advisory Council on the Misuse of Drugs (ACMD), 2016).

1.7 What About Other Fields?

This issue is not only capturing the attention of concerned users, family and friends, clinicians in mental health, acute care, as well as global agencies, governments and public health officials, but also other allied health fields. There is an increase in attention across disciplines that deal with chronic pain (non-cancer particularly), palliative care, anaesthesiology, respiratory medicine and sleep medicine. Further, these fields are not simply discussing the issues around opioid use within their standard clinical practices but wider issues pertaining to addiction.

One pertinent example is in the field of anaesthesia. In 2006 and 2011, American multidisciplinary conferences were organised to address the issue of opioid-induced respiratory impairment. In the last two to three years, the issue is more prominent in anaesthesia literature and there is an obvious increase in concern given the recent crisis. The issue for this field has been the inconsistent recording of the physiological measures of overdose, and respiratory depression. The literature states that taxonomy and outcome measures need to be standardised, and monitoring tools and measures need to be determined as appropriate for reducing opioid-induced respiratory depression (Gupta & Edwards, 2018).

Opioid-induced respiratory depression is challenging to measure reliably. There are also evident difficulties in testing new monitoring techniques or technologies. Comparison to other, previous studies is also a challenge because respiratory depression is defined differently (Gupta & Edwards, 2018; Jungquist, Karan, & Perlis, 2011). The conclusions of these meetings were that, until a more reliable tool existed, the simplest method, continuous pulse oximetry, would be implemented. This is related to one of the most critical questions that underlies the thesis: how can we reliably detect and measure respiratory depression?

Summary

With global upward trends and new record figures in some countries, the issue of drug-related deaths requires attention. The USA is experiencing the most severe crisis, with drug overdose appearing to be the leading cause of death for people under the age of 50, and with 91 deaths per day (Rudd et al., 2016). The UK has seen a distinct rise in recent years, with Scotland now leading the number of deaths per capita in Europe, at 160 deaths per million (NRS (National Records of Scotland), 2018). Unfortunately, there does not appear to be any sign that these figures will diminish any time soon. This thesis intends to explore some of the risk factors thought to play a role in opioid overdose using novel and physiological techniques. The work presented in this thesis should serve as the foundation for future studies that could eventually prevent these deaths.

2 Heroin Through History

2.1 Preface

The UK has a long history of prescribing pharmaceutical heroin (diamorphine). In fact, diamorphine prescribing was one of the main forms of treatment for heroin addiction in the UK (the 'British System'), particularly after the late 1950s and up until the mid-1970s. Thereafter, the growing reputation of oral methadone led to its dominance from the late-1970s onwards. Within the context of this thesis, has the UK always had high mortality rates from heroin overdose?

This chapter will guide the reader through the history of diamorphine prescribing practices and focus on reports on mortality rates through this period and subsequently to comparable studies in the present day. As is often debated within the addictions and drug policy fields, a key question arises: do pharmaceutical, prescribed drugs increase safety for the user compared to illicit drugs of unknown purity? This will be explored in the chapter and represents an opportunity to uncover data that exist in this unique time period. This chapter also describes the special opportunity that the UK provides in studying opioid overdose and contextualises the history of mortality data and opioid overdose research.

I presented some of the data in this chapter at the 1st Lisbon Addictions conference in September 2015 as well as at the Institute of Psychiatry, Psychology & Neuroscience PhD symposium in May 2015. It is planned that a version of this chapter will also become a journal article (post-PhD).

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2.2 Background

2.2.1 What is the 'British System' and When was it Truly Active?

The ethos of the British approach to pharmaceutical heroin prescribing, which became known as the 'British System', was confirmed by the Rolleston Committee recommendations of 1926. The Rolleston Committee concluded that addiction should be considered a medical problem rather than a criminal and moral one, with doctors permitted to treat and maintain patients with diagnosed opiate addiction, i.e. to prescribe medicines such as morphine or heroin to prevent the emergence of withdrawal symptoms and to continue this prescribing if withdrawal of the medicine led to ongoing distress (Rolleston Committee, 1926).

The British System approach continued for decades. The Second Report of the Brain Committee (1965), and the subsequent changes to the drug laws in 1968 continued to allow doctors to prescribe (injectable) heroin for the treatment of addiction although the 1968 legislation restricted the medical authority to prescribe pharmaceutical heroin to the new cadre of doctors working in the newly established drug dependence clinics. Further, a new system of notification[1] of addicts to the Home Office by doctors became mandatory after 1968, modelled on systems of compulsory notification of infectious diseases (Ghodse et al., 1985).

2.2.2 1960 to 1975

In the decades leading up to the 1950s, in the UK, the number of opiate addicts was modest at around 400-600 in any one year and they were almost all considered 'therapeutic addicts', because they had become addicted whilst being treated for pain from a physical disorder (Spear, 1969). This group also included doctors or other professionals (e.g. pharmacists) who had access to these opioid drugs. Only a small proportion were addicted to heroin, and all were middle-aged or over (Spear, 1994; Connell & Strang, 1994).

[1] The Addicts Index was a notification system of addicts as a method of the Home Office keeping track of the number of addicts that entered treatment or were seen by doctors.

After 1951, a new group of heroin addicts began to emerge, mainly in London (Spear & Glatt, 1971; Spear, 1969). These heroin users had begun their heroin use by buying diverted or stolen supplies of pharmaceutical heroin (Spear, 1994). Many of these new heroin users were young and also sometimes engaged in delinquent behaviours. Between 1960 and 1968, a small number of doctors in the inner London area (probably never more than half a dozen at any single point in time) were prescribing significant amounts of heroin for what might be considered non-therapeutic purposes or solely for treatment of their patients' addiction (i.e. to 'non-therapeutic addicts') (Leech, 1981; Spear, 1994). The number of known heroin addicts was only 62 in 1958 but grew to 324 by 1964. The pattern of prescribing (i.e. high doses) by these doctors was described at the time as "lunatic generosity" (Brain Committee, 1965) and created a considerable illicit market from the surplus doses prescribed. However, this illicit market, along with all heroin in the UK, was comprised of pharmaceutical diamorphine (heroin) exclusively (Cooke, 1962; Frankau, 1964) (i.e. no illicitly-imported heroin). This did not substantially change until the mid/late-1970s when significant amounts of imported heroin from the Middle East region became available in the UK for the first time.

Injectable prescribing continued as the first-line treatment for heroin addiction until its peak in the mid-1970s (Strang et al., 1994), and then tapered off through the late 1970s, 1980s and thereafter (Strang & Sheridan, 2006). This can be evidenced by gradual changes in the actual quantities of prescribed injectable heroin, injectable methadone and oral methadone during this time period (Mitcheson, 1994; Strang et al., 1994). This shift in prescribing patterns was also discussed by Hartnoll and colleagues in their trial on the acceptance of two types of heroin addiction treatment: injectable heroin maintenance versus oral methadone maintenance (Hartnoll et al., 1980). Consequently, in this chapter, 1975 is the cut-off date for the end of the study period of this distinctive era of dominance of pharmaceutical diamorphine as the available form of heroin in the UK.

Over this period (from early 1960s to mid-1970s), diamorphine prescribing was the mainstay form of treatment for heroin addiction. Furthermore, there was a low threshold for patients to obtain a diamorphine prescription, and generally, during the 'British System', diamorphine maintenance was the preferred and most acceptable method of dealing with heroin addiction (Spear, 1994; Strang et al., 1994).

2.2.3 Opening of Clinics

Plans for the opening of new clinics started in 1967 by the Ministry of Health. The aim of the new clinics was to “contain the spread of heroin addiction by continuing to supply the drug in minimum quantities where this is necessary in the opinion of the doctor, and where possible to persuade addicts to accept withdrawal treatment” (Ministry of Health, 1967).

Fifteen new outpatient clinics first opened across London. A smaller number opened up in the Home Counties and few specialist clinics existed elsewhere in the UK. Whilst a degree of freedom existed, at least compared to today’s standards, in terms of take-home supplies, injectable drugs and fixing rooms with free equipment, the level of control introduced was definitely intensified (Connell & Strang, 1994). These were as follows:

- Necessity to attend weekly or fortnightly appointments at the clinic;
- Requirement to collect drugs on a daily basis from a local community pharmacist.

The main complication was the necessity to balance competing responsibilities: good quality treatment of the individual patient versus the concern about the broader social and public health perspective. The main premise of these changes was to prevent the extra supply of heroin on the black market. Additionally, there was still only a small amount of oral methadone initially.

2.2.4 What was the Mortality Rate During the Era 1960 to 1975, During the British System?

The mortality rate during this period of readily available pharmaceutical diamorphine (with only very rare appearance of illicitly manufactured, imported heroin) is thus of interest. We are able to examine mortality data through the case studies and reports from clinics from a time that has now ceased to exist in the UK, and the rest of the world. It is a distinctive opportunity to examine this prescribing practice which is still being discussed today. Hence, the information presented here should be added to this debate on mortality and opioid prescribing.

2.2.5 After the Mid-1970s

The mid-1970s was the time point at which, for the first time, more oral methadone was prescribed than injectable heroin. Total quantities of prescribed injectable heroin, injectable methadone and oral methadone reveal a gradual transition from the late 1960s onwards. In 1970, 17kg, 11kg and 3kg of injectable heroin, injectable methadone and oral methadone, respectively were being prescribed. This became 15kg, 21kg and 8kg, respectively by 1974, and then 9kg, 14kg and 17kg by 1978 (Figure 2-1, Strang et al. 1994). Calculations of a mean dose of opiates per patient were collated for each clinic during the period of 1968 and 1980. This further supported the observation that there was, over this period, a gradual shift of prescribing patterns particularly during the early 1970s.

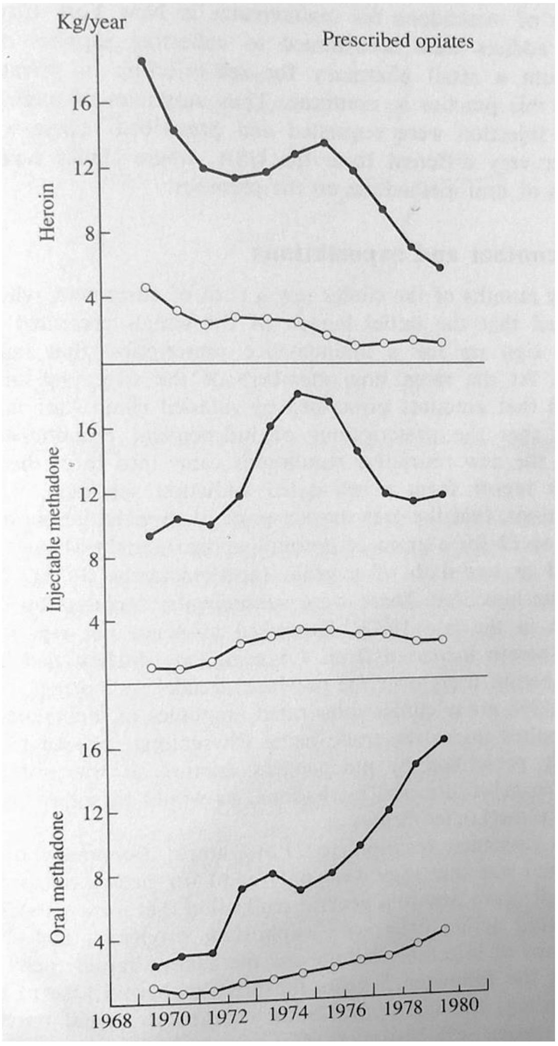

Figure 2-1: Clinic Return to Department of Health (Mitcheson, 1994). ● London; ○ Elsewhere.

The data presented in this chapter focus on the mortality rates of heroin users who received diamorphine maintenance treatment during the time period of 1960 to 1975 (Appendix A-1), as described in cohort studies from the various clinics, mostly in London. The focus of the original studies was not specifically on mortality but rather was more usually a follow-up or evaluation study of a cohort of patients from the clinics, or of patients registered as addicts with the Home Office. Some of these studies included mortality data as part of their follow-up, and thus re-examination is meaningful. By examining the literature for this time period, the prescribing of pharmaceutical diamorphine, and its potential impact on mortality in the treated population, can be investigated.

2.3 Methods

2.3.1 Data Sources and Search Strategy

Searches were performed of the English-language literature indexed in Embase, Medline and PsycINFO (1960-1978). A wide year range was set in order to ensure capture of studies that recruited within the period of interest of between 1960 and 1975. Furthermore, a wide-ranging set of terms was used in order to maximise sensitivity. Combinations of keywords included 'heroin dependence', 'drug dependence', 'opiate addiction', 'opiate maintenance', 'heroin treatment', 'heroin' or 'opiate', 'follow-up', 'observation', 'mortality', and 'death'.

A full list of search terms and sequence of queries is listed in the appendix (Appendix A). Historical papers are not always reliably tagged with keywords nor do they always include an abstract, and thus, a broad search was required in order to ensure that all potentially relevant records were captured. Hand-searches of the personal libraries was also made of several experts in the field were made to check against bibliographies of articles, which were also examined for citations. Key informant enquiries were also made with experts within the field. The types of articles that met the inclusion criteria (see appendix: A-3) were observational, follow-up and case reports of clinical data. Papers that focused on heroin users in any form of treatment were reviewed.

2.3.2 Data Extraction and Synthesis

Duplicates and non-English language papers were removed. Papers were then subject to a review by title. A further review was based on abstracts. Full-text articles were then examined, and relevant papers and data were extracted (see appendix: A-2).

Extracted data included recruitment years, study length (or follow-up period), mortality in absolute numbers (or percentage), type of treatment available and other demographics (if available). Annual mortality rates were calculated using the mortality figures listed in the paper but normalised across all papers to calculate a mortality rate per year, based on the period of recruitment of the studies.

2.4 Results

Database and hand searches resulted in 4,679 records in total, from which 15 relevant publications were identified (Table 2-1). Out of these 15 publications, some reports were related to the same cohorts. Four publications related to a cohort study originally reported by Stimson and Ogborne (1970). Two publications were related to one cohort (Chapple, Somekh, & Taylor, 1972b) and two reports related to a separate cohort from d'Orbán (1973). All seven other reports were from cohorts of patients.

All 15 reports described patients recruited from clinics, hospitals and surgeries based in London or near to London (only one study was based outside, but near, London, in Surrey (Beckett & Lodge, 1971)). At this time, these types of clinics were limited in areas outside of London.

2.4.1 (A) Raw Data on Mortality Rates at Follow-up

The paper at the start of this time period, Frankau (1964), was a report of follow-up of a total of 50 Canadian addicts from a clinic in West London. After an initial stabilisation period, withdrawal treatment occurred. Ten of 50 had become addicted whilst in Europe and were financially stable. Forty of the patients came to England specifically to seek treatment for their heroin addiction. Of these 40, one died and the status of four could not be ascertained. Thus, a minimal mortality rate for this study was 2% over the study period of 5 years.

Two studies from a cohort of female addicts in prison followed up at 12 and 48 months showed mortality rates of 3% and 15% respectively over the study periods (d'Orbán, 1973; d' Orban, 1970).

The highest mortality rate was seen in the earlier studies during the recruiting period of interest. In one study which provided follow-up at 6 months, there was a 15% mortality rate (thus 30% as an annual mortality figure), albeit in a very small cohort of 33 patients (Bewley, 1965). They were recruited from various London hospitals and were considered by the author as being "disturbed and difficult to treat" with seven admissions to hospitals between them.

However, a similar cohort of heroin addicts admitted to ‘mental’ hospital as inpatients actually reported no deaths in their 7 to 19 month follow-up (Beckett & Lodge, 1971). An additional study of adolescents who were referred to a special treatment unit and followed up for 12 months also reported no deaths (Boyd, Layland, & Crickmay, 1971).

Studies on hospital admissions related to patients for whom heroin prescribing was the dominant form of treatment had a variety of high mortality rates. Bewley & Ben-Arie (1968) reported an average mortality of 9.5% after 20 months, and the Chapple studies (Chapple et al., 1972a; Chapple et al., 1972b Table 2-2) reported 8% at 1 year, 16% at 5 years and 18% at 6/7 years.

Outpatient treatment centres appeared to have a more consistent outcome on mortality. The four studies associated with Ogborne & Stimson (Table 2-2) showed mortality of 4%, 6.2%, 9% and 12% when followed up at 1, 3.5/4, 6 and 7 years, respectively (Stimson, 1973; Ogborne & Stimson, 1975; Thorley et al., 1977; Stimson et al., 1978). Bewley et al. (1972) followed up 397 patients after 1 year and found a mortality rate of 2%.

Another study by Bewley et al. followed up 259 newly notified addicts through the Home Office Addicts Index (Bewley et al., 1968) and found a mortality rate of 3% over the 12 months of study.

2.4.2 (B) Calculations of Annualised Mortality Rates

For the next step in this examination, I have calculated the average annual mortality rate. Whilst statistical weaknesses need to be acknowledged (since this assumes constant risk over time and also through different stages of addiction and of treatment), it nevertheless allows an overall examination, across studies, of the range of mortality rates observed. Estimated annual mortality rates, calculated with respect to the follow-up period, varied greatly. The follow-up was often conducted over a period of time, over a span of a year in some cases, thus the annual mortality rates in these cases have been provided also as a range. The majority (13) of the publications had an estimated annual mortality rate of between 0% and 4% (Beckett &

Lodge, 1971; Bewley et al., 1968, 1972; Boyd et al., 1971; Chapple et al., 1972a, 1972b; Frankau, 1964; Ogborne et al., 1975; Stimson et al., 1978; Stimson, 1973; Thorley et al., 1977). The remaining two had 9.5% and 30% (Bewley, 1965; Bewley & Ben-Arie, 1968). The median annual mortality rate of the 10 reports[2] for this time period was 2.4% and the average was 5.4%.

For studies which reported at more than one point in time, it was also possible to examine how mortality rate in a cohort might change over time. These studies of the same cohort saw a progressive reduction in mortality rate over time. An estimated annual mortality rate of 8% was seen in the first year of the Chapple study. By the 5-year follow-up observed, the annual average had reduced to 3.2%, and by the 6/7-year follow-up, the figure was 2.8%, as an average (Chapple et al., 1972a, Table 2-2). Furthermore, the Stimson & Ogborne cohort studies found an initial 4% annual mortality rate after the first year of follow-up and then a fluctuating rate of between 1.5% and 2% at every subsequent time point (Table 2-2). However, in contrast, the d'Orban studies that followed up female addicts in prison at 1-year and then 4 years saw annual mortality figures of 3% and 3.8%, respectively (Table 2-2).

There were two additional papers that were excluded from the main studies because they extended outside the selected 1960-1975 era; however they still had overlapping recruitment periods with the time period of interest of this study (Table 2-3). Oppenheimer (1994) re-examined the Ogborne & Stimson cohort 22 years later (see also Table 2-2) where it was found that 38% of the whole cohort had died by the 22-year mark. The second paper was James (1967) which showed that, of the 450 addicts notified to the Home Office, 35 died within the years 1955 to 1965 resulting in a 9% mortality of the cohort and an estimated annual mortality rate of 0.9%. However, part of the recruitment period is not relevant for this study and thus is not analysed further.

[2] Where multiple publications from the same cohort exist, only the most recent publication is included, thus 10 reports are used for the overall analysis.

Table 2-1: Studies included for examination. Additional publications of the same cohort in italics. Only most recent publications of each cohort are included in the calculation of annual mortality rates (as indicated by *).

Study	Sample Size	Years Recruited	Follow-up period in months	Mortality %	Annual Mortality % (range)	Type of Treatment
Frankau (1964)*	50	1959-64	60	2	0.4	Private practice. Follow-up of Canadian addicts in London
Bewley (1965)*	33	1964-65	6	15	30	Admissions to a number of London ‘mental’ hospitals - considered as 'difficult to treat'
Bewley & Ben-Arie (1968)*	100	1964-66	12 to 27	13	9.5 (13 to 6)	Patients discharged from South London hosp.
Bewley et al (1968)*	259	1965	12	3.4	3.4	Follow-up of newly notified addicts
Beckett and Lodge (1971)*	34	1966	7 to 19	0	0	Various - inpatients (sectioned or otherwise)
Boyd et al.,(1971)*	78	1968	12	0	0	Adolescents referred to a special treatment unit
Chapple et al (1972a)	108	1963-65	60 (12)	16 (8)	3.2 (8.3)	Several hospitals. Includes 'therapeutic prescribing' as treatment (12-month data).
*Chapple et al (1972b)**	*108*	*1963-65*	*72 to 84*	*18*	*2.8 (2.5 to 3)*	*Same as above.*
Bewley et al (1972)*	397	1968-69	12	2	2	Outpatients at 3 London hospitals.
Stimson (1973)	101	1969	12	4	4	Cohort at London Drug Dependency Treatment Centres. Patient status from Home Office Records. Original cohort (n=128) in Stimson & Ogborne 1970.
Ogborne & Stimson (1975)	*128*	*1969*	*42 to 48*	*6.2*	*1.7 (1.6 to 1.8)*	*Same as above.*
Thorley et al (1977)	*128*	*1969*	*72*	*9*	*1.5*	*Same as above.*
*Stimson (1978)**	*124*	*1969*	*84*	*12*	*2*	*Same as above.*
d’Orban (1970)	66	1967-68	12	3	3	Female addicts in prison
*d’Orban (1973)**	*60*	*1967-68*	*48*	*15*	*3.8*	*Same as above.*

Study	Sample Size	Years Recruited	Follow-up period (months)	Mortality %	Annual Mortality % (range)	Further Information
Results from the 1969 Stimon & Ogborne cohort (1970):						
Stimson (1973)	101	1969	12	4	4	Status of patients from Home Office Records. 101 (of sample of 128) interviewed 1 year later. Range of dose 10-1140mg
Ogborne & Stimson (1975)	128	1969	42 to 48	6.2	1.7 (1.6 to 1.8)	Follow-up 3.5 to 4 years after initial interview
Thorley et al (1977)	128	1969	72	9	1.5	6-year follow-up
Stimson (1978)	128	1969	84	12	2	7-year follow-up
Oppenheimer (1994)	128	1969	264	38	1.8	22-year follow-up
Results from the Chapple et al cohort (1972):						
Chapple et al, (1972a)	108	1963-65	60	16	3.2	Also mentioned within this paper: 1-year follow-up presented with mortality level of 8.3%
Chapple et al (1972b)	108	1963-65	72	18	3	6-year follow-up
Results from the d'Orban cohort (1973):						
d'Orban (1970)	66	1967-68	12	3	3	Full cohort sample
d'Orban (1973)	60	1967-68	48	15	3.8	After 1-year follow-up, 6 participants were omitted as they were classified uncertain

Table 2-2: Results from the three cohort studies.

Table 2-3: Related studies with overlapping recruitment periods.

Study	Sample Size	Years Recruited	Follow-up period (months)	Mortality %	Annual Mortality (%)	Type of Treatment
James (1967)	450	1955-1964	120	9	0.9	Heroin addicts known to Home Office
Oppenheimer (1994)	128	1969	264	38	1.8	22-year follow-up of cohort from Stimson & Ogborne 1970

2.5 Discussion

From the 1960s to the mid-1970s, take-home heroin prescribing was the main form of treatment for heroin addiction in the UK (the 'British System'). Retrospective analysis of mortality of treated cohorts over this period is possible due to the existence of observational and follow-up studies of clinics in England at this time. Data from these studies showed that the heroin-prescribed population during the late-1960s to mid-1970s of the ‘British System’ had substantial mortality. However, this varied greatly; in some clinics there were few or no deaths at all, whereas in other clinics, much higher mortality rates were seen.

2.5.1 Annual Mortality Rates

Exploring this annually, the figures differ as the duration of the studies vary. The majority of studies (nine) had an annual mortality rate of between 2% and 4%. The Bewley (1965) study is an outlier with an annual figure of 30%. However, this study has the smallest cohort and the shortest recruitment period when compared with the other studies in this chapter, and this could explain the ‘outlier’ status of the observed mortality rate.

The differences cited in annual mortality rates across studies with the same cohort are interesting to note. Chapple et al (1972) state the reason for the difference between their 1-year and 5-year observations is because of the circumstances of referral; some patients included in the study had died during the initial hospital admission. The Ogborne & Stimson cohort (Table 2-2) was another interesting cohort. They also saw an initially higher mortality rate but it remained at below 2% after the 1-year mark. This cohort was also followed up much later at which point it was found that the mortality rate remained at an average of 1.6% per year (Oppenheimer et al., 1994).

2.5.2 Explanations for Mortality Rates and Wider Implications

Some studies of that time make reference to the beginnings of imported heroin (from China) and promote this as a possible reason for drop-outs from treatment and death rates; the former due to easier access to the illicit market, and the latter due to adulteration. However, adulteration was unlikely to have been a factor (for the deaths reported above) for a number of reasons, not least because the imported heroin was only just beginning to enter the English drug market and was in a completely different form – as loose powder, compared with the pharmaceutical diamorphine which was mostly in tablet form.

It is necessary also to consider mortality of heroin users at this time in other countries and global mortality figures of heroin users are available. The mortality rate described in the USA by an influential 20-year follow-up study was at around 10 per 1,000 per year, or 1% annually, during the 1960s (Vaillant, 1973). In New York, around 350 deaths were occurring among 35,000 addicts (Helpern & Rho, 1966; Louria et al., 1967), again with an annual mortality rate of 10 per 1,000 (i.e. 1% annually). It is important to note that diamorphine maintenance was not available as a treatment in the USA and indeed there was very little medication-based treatment of any type in the USA, at that time, and certainly no maintenance treatments. Comparing the UK figures with these mortality figures is interesting. A difference of 1% and 5.4% is notable. Certainly the 'British System' of heroin prescribing did not seem to prevent the high annual mortality.

2.5.3 After the Mid-1970s

After the period examined in this chapter, there was a dominance of methadone maintenance treatment in the UK, and death rates were generally lower but still varied (Oppenheimer et al., 1994). Studies outside the UK after this time seemed to show that death rates depended on the type of treatment. Detox treatments and restrictive treatments (such as those that expel people from treatment for violating the regime) appeared to show higher rates of mortality, for example, in Sweden and the USA (Gronbladh et al., 1990; Gearing et al., 1977; Fugelstad et al., 1989). In the UK, an excessive death rate was observed in the mid-1980s (Table 2-4 and Figure 2-2) and it was suggested that this was connected to the import of heroin on the black market and when clinic policy became 'less generous' (Oppenheimer et al., 1994). A large proportion of these deaths were overdoses, and it remains a possible explanation that the mortality figures may have been affected by treatment regimes (Oppenheimer, 1994).

One of the largest follow-up cohort studies examined in this chapter was the Ogborne &

Stimson cohort, between 1969 and 1991. They examined the excess mortality ratios which were calculated based on the ratio of the number of deaths observed to the numbers expected to die in an age- and sex-matched sample of the general population over a similar period. Of those who were recruited in 1969, 38% had died by 1991. 58% of those who died were most likely using at the time of their death, and overdose was by far the largest single category of death. Only 22% of the overdose cases mentioned an opiate as the only drug on the death certificate, and 55% contained multiple drugs. There were no deaths in this cohort from HIV/AIDS.

Table 2-4: Mortality rates over the period 1969 to 1991(Oppenheimer et al., 1994).

Years	Time in study	Deaths (cumulative)	Years at risk	Mortality rate per annum (%)
1969-1970	2	4	2262	2.12
1971-1976	6	15	8526	1.55
1977-1982	6	25	7755	1.55
1983-1988	6	40	6830	2.64
1989-1991	3	43	2612	1.38

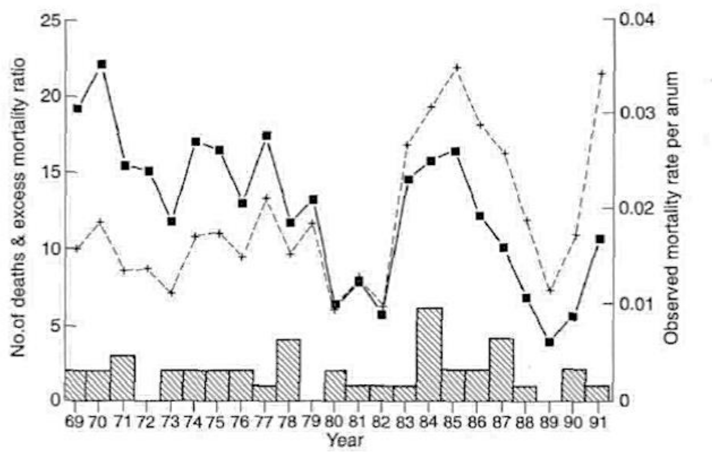

Figure 2-2: Mortality in 128 heroin addicts 1969-1991 rates per annum (average over 3 years) …+… observed mortality; ■ excess mortality ratio; ▣ actual deaths (Oppenheimer et al., 1994).

This demonstrates that from the 1970s onwards, it became more complex and difficult to unpick the underlying causes of opioid-related mortality. Historical data allows us to highlight periods of time where potential confounding factors such as the illicit drug market fluctuations or changes and nuances in clinical treatments are known to not have been significant.

2.5.4 Present Day

Current heroin maintenance treatment is mostly conducted in supervised heroin clinics and has now been extensively studied in randomised controlled trials (Strang et al., 2012). In contrast to the mortality rates evident in the much earlier studies of unsupervised heroin prescription of the 'British System' of the 1960s and early 1970s, the new generation of supervised heroin clinics have extremely low rates of mortality compared to the majority of the studies presented here. In a recent systematic review of randomised controlled trials of existing studies, total mortality events was found to be 0.7% across all the trials that were examined (Strang et al., 2015). This is much lower than the rates seen in the publications presented in this chapter, even though the patients recruited to the new supervised heroin clinics are specifically selected as 'difficult to treat'. The story of mortality rates outside of this small refractory-treated population is remarkably different, as addressed in chapter 1.

2.5.5 Strengths and Weaknesses of the Evidence Examined in this Chapter

This chapter uniquely examines a time period where diamorphine prescribing was the prevailing form of treatment of heroin addiction in the UK. The prescribing habits of that time have ceased to exist, and yet, discussion of heroin prescribing as a maintenance treatment continues. The mortality data presented here can contribute to this debate and expand our understanding of diamorphine prescribing and to opioid overdose mortality. However, caution should be exercised in generalising these mortality data. A reliable and comparable cohort of non-treated addicts, i.e. addicts who did not enter treatment and were not prescribed pharmaceutical heroin for maintenance treatment of heroin addiction, does not exist from this time period. As described previously, registration of addicts by the treating clinic or hospitals to the Home Office existed throughout this time period (and as a legal requirement from 1968 onwards), and the numbers of non-registered addicts was very few (Frankau, 1964; Spear, 1994). Thus, care should be taken when extrapolating the findings presented to other contexts and other points in time. Nevertheless the data, and consideration of their implications, give a valuable point of reference.

Take-home heroin as a mainstay treatment for heroin addiction along with the influences of illicit and licit forms of pharmaceutical heroin have been the source of numerous contentious debates. The data presented in this paper should be considered as an opportunistic re-examination of the relationship between heroin and mortality, and should be deliberated upon with curiosity and caution, alongside the interest.

The heroin being used in the UK over the period of focus of this chapter was pharmaceutical. The surprising finding, with regard to mortality, is that the proportion of heroin-related mortality which occurred in the treated population during the 1960s to mid-1970s of the 'British System' was comparable to, or greater than, the mortality rates reported in the international literature for the untreated population and substantially greater than the currently reported <1% annual mortality with oral opioid treatments.

2.6 Implications for thesis

2.6.1 The UK's Special Position in the Study of Opioid Overdose

For most of the 20th Century, after the closure of heroin clinics in the USA in the early 1920s, the UK was the only country in which heroin was prescribed, up until the establishment of the new form of supervised heroin treatment centres in Switzerland in the 1990s. By 2015, there were eight countries in the world that provided diamorphine treatment as maintenance treatment for heroin addiction: Switzerland, The Netherlands, Spain, Germany, Belgium, Denmark, Canada and England (Strang et al., 2015). Except Spain, all of these countries still continue to provide injectable diamorphine or injectable opioid treatment as part of continued research trials or as part of their health service to patients.

In England and the UK, the new form of supervised heroin treatment was the subject of study in the Randomised Injectable Opiate Treatment Trial (RIOTT). Following the trial, central government funding was provided for this supervised heroin treatment from three centres, but central funding was not continued beyond 2014 and local funding was not provided: consequently, these clinics closed in 2015. Nonetheless, a small amount of diamorphine prescribing still continues in the UK in the older unsupervised approach, and there is discussion, or implementation, of supervised diamorphine-maintenance clinics in Scotland and the North East of England (Alderson, 2017; Siddique, 2017). In 2017, over 100,000 items of diamorphine were dispensed[3], however, these included diamorphine for the use in non-addiction treatment practices such as operative and palliative cases, and so it is difficult to gauge the extent of heroin treatment for addiction across the UK – it is thought to be less than 100 patients in total.

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[3] Data for this are provided by Open Prescribing (OpenPrescribing, 2017) which provides data on prescribed medication by the NHS. It is currently not possible to determine how many of these diamorphine items were prescribed for the use in heroin addiction treatment.

NB: Open Prescribing define 'item' as follows: *'A prescription item is a single supply of a medicine, dressing or appliance written on a prescription form. If a prescription form includes three medicines it is counted as three prescription items. Item figures do not provide any indication of the length of treatment or quantity of medicine prescribed.'*

Out of the eight countries that prescribe diamorphine for heroin addiction, the UK is actually the only country that gives diamorphine full approval as a medicinal product, i.e. it is used in addition to maintenance treatment medication and has been for many decades. The majority of other countries (Germany, Switzerland, Canada, The Netherlands, Belgium and Denmark) approve diamorphine specifically as a medicinal product for 'treatment-refractory' heroin dependence (Strang et al., 2015). Further, Spain and Belgium approved diamorphine as a specific investigational medication for use in research trials. All other countries in the world completely prohibit the use of diamorphine for use in treatment and/or have blocked or not granted heroin-prescribing research trials, such as is the case in the USA, Australia and France (Strang et al., 2015).

With the limited number of clinics and legislations that allow use of diamorphine as part of heroin addiction treatment, there are very few opportunities to study opioid overdose with people who are actually taking diamorphine in a manner that is safe and ethically sound. While there are discussions of new clinics and trials emerging, even in regions of the world where it was never thought possible, e.g. the USA[4], this is still an extremely limited form of heroin addiction treatment. It is clearly a unique position that the UK is able to provide such an opportunity for special study of the effects of diamorphine administration.

2.6.2 Study of Opioid Overdose Through History

As with most studies of drugs that have potentially lethal adverse effects, the clinical study of opioid overdose is experimental and requires attention to reduce risk. However, this thesis investigates what causes respiratory depression, and why some people appear to be more vulnerable than others. These questions are not in and of themselves novel, these issues have arisen before, in crises and epidemics around the world. The question that is important but rarely considered is why have there been so few similar studies to date? The likely answer is that they have not been examined precisely because of the very nature of the drug being studied (i.e. heroin). There is something circular and counter-productive about this situation.

[4] In the USA, there is only yet discussion of this topic. The RAND corporation are currently conducting a study into possibility of initiating supervised injectable heroin treatment programmes (Kilmer, 2018).

Because of public and regulatory concerns about heroin, it is, for example, almost impossible for researchers in the USA to study the effects of diamorphine. Indeed, in the statement from the independent scientific committee at the UNODC 61st Committee on Narcotic Drugs meeting of 2018, a recommendation was recently made that:

> Facilitating research with controlled substances, including synthetic opioids, to generate new knowledge on how to use these substances to revert overdoses or adverse effects. As stated in the UN Conventions, controlled substances should be available for medical and scientific purposes, thus barriers to conducting such research should be removed.

Historically, trends of drug use and mortality in the USA have often been focused on because of the potential influential effect on the UK. However, while similarities have been seen previously, particularly amongst heroin use in the 1960s onwards (Gfroerer & Brodsky, 1992), this has not always been the case. At this point in time, there is growing concern amongst those in the field about the influx and dangers of fentanyl which stems from the considerable increase in deaths observed in the USA in the last two years that have been, in large part, attributed to fentanyl and its synthetic analogues/derivatives (Hedegaard et al., 2017; Seth et al., 2018). While it is difficult to predict whether the UK will have the same fate – there have only been a small number of deaths from fentanyl reported so far (UNODC, 2017) – there is good reason to be cautious. However, this should provide the impetus for further debate and further research above all else.

This chapter has provided the opportunity to examine historical data not simply as a retrospective opportunity to re-examine data but to reflect on trends and concerns that have been raised previously and to learn from them. It is with great hope that in a further 50 years progress will have been made of the kind that takes our understanding beyond the stagnation that has characterised the field over the past half century. We will most likely never observe the situation that existed prior to the 1970s in the UK and hence it is vital to learn as much as possible from retrospective examination of data from this earlier era and to consider their relevance to the situation of today.

3 An Overview of Overdose Mechanisms and Respiratory Physiology

3.1 Preface

This chapter reviews the literature on opioids and opioid-related overdose and the current understanding of overdose mechanisms, respiratory physiology and relationship with lung disease. In addition, it raises some of the questions that are driving future research. Demographic and epidemiological data on overdose are extensive and valuable, however, clinical data are still lacking in certain areas. The potential dangerousness of opioid drugs is evident in the effects on the respiratory system. Overdoses are obviously complex but investigations into the mechanisms of fatalities and near fatalities are vital in the future prevention of overdose deaths.

Part one provides an overview of pharmacodynamics (how opioids affect the body and their mechanism of action) and pharmacokinetics (the movement of the opioid drugs through the body). Part one also discusses the evidence for risk factors of opioid overdose from robust epidemiological studies and proposed contributory mechanisms. **Part two** details the physiological aspects of the respiratory system and its functioning, from a broad description of the anatomy and function of the respiratory system and subsequently, the relevant details involved in the mechanisms surrounding breathing and the effects of opioids on these mechanisms. **Part three** describes the overarching public health issues that this thesis is concerned with. Finally, **part four** ends on how respiratory depression can be measured and provides rationale for the various criteria that are used throughout this thesis.

The respiratory system is a central aspect of this thesis and the purpose of this is in relation to the techniques that are used to detect acute overdose in this PhD. These techniques involve novel and accurate measurements of respiratory function and of respiratory muscles. An understanding of the function of the normal respiratory system is also central to understanding the relationship between overdose risk and underlying respiratory disease, a relationship that has not previously been explored in detail.

I had the opportunity to author a chapter within the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) Insights report on ‘Preventing Opioid Overdose Deaths with Take-Home Naloxone’. This chapter incorporates the content from my co-first-authored initial chapter of the report (‘Pharmacology and physiological mechanisms of opioid overdose and reversal’, p.15-28, EMCDDA, 2016).

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Part 1: A Recipe for Overdose.

3.2 What are Opioids?

The terms ‘opiate’ and ‘opioid’ are sometimes used interchangeably, but, in pharmacology, the term ‘opiate’ describes any of the opioid analgesic chemicals found as natural products in the opium poppy plant, *Papaver somniferum* (Shook, 1990). Both opiates and opioids have been used medicinally predominantly for pain relief, but also for their strong sedative (sleep disorders), anxiolytic (reducing anxiety), anti-tussive (cough suppressant) and anti-diarrheal properties. Since the nineteenth century, it has been possible to obtain opiate products through the chemical isolation and extraction of the active ingredient from the opium poppy plant (Berridge, 1999). Major opium alkaloids are morphine, codeine, and thebaine, of which morphine and codeine have analgesic properties and depressant effects, while thebaine has no direct therapeutic effect.

Heroin, which has the chemical name diacetylmorphine (also called diamorphine) is produced by a simple chemical reaction from morphine. The chemical processes of converting opium into diacetylmorphine (i.e. diamorphine or heroin) involve processing opium into morphine before acetylation to produce heroin (Lerner & Mills, 1963). Heroin was originally discovered in St Mary’s Hospital, London, by Wright and Beckett. In their 1874 and 1875 papers describing a series of experimental studies on natural alkaloids, diamorphine is referred to as ‘tetra acetyl-morphine’, an acetylated version of morphine (Beckett & Wright, 1875; Wright, 1874). This discovery did not develop any further and around 20 years later, diamorphine was re-synthesised in Germany, and marketed in 1898 by the chemical company Bayer under the trade name ‘Heroin’.

The term opioid is a wider term that includes the semi-synthetic analogues such as methadone and buprenorphine and also, heroin. The term opioid also encompasses the endogenous opioids, naturally occurring opiate and opiate-like drugs, including molecules that are very different from natural opiates but which nevertheless activate the opioid receptors in the human body, producing similar effects to natural opiates (e.g. endorphins).

With regard to effects of opioids, some people experience a euphoric reaction to opioid medications, as opioids also affect the areas of the brain involved in the reward system (NIDA, 2014). Their potent medicinal effects as well as their euphoric properties may explain why the opioids are among the most commonly used groups of drugs for recreational and self-medication purposes. The distinct properties of opioids that will be explored in this chapter can lead to physical and psychological dependence, and also carry a high risk of overdose.

Most of the heroin currently found illicitly in Europe is in the form of a brown powder (base) which originates from South-West Asia (Ciccarone, 2009). The base is not water-soluble but is suitable for vaporisation with heat (known as 'chasing' but sometimes also called 'smoking', although no combustion of heroin takes place). It requires an acidifier (e.g. vitamin C) and heat to dissolve it in water and allow it to be injected. The white powder (salt) form of heroin, traditionally originating from South-East Asia, is soluble in water and can more easily be injected (although this often still requires heat) (Ciccarone, 2009).

3.3 How do Heroin and Other Opioids Work?

Heroin and the opioids affect several different areas in the human body. The primary areas of action are the brain, spinal cord and gastrointestinal tract, where the opioids bind to receptors in the nervous system and produce their actions through processes of activation or inhibition. Opioid receptors act in controlling physiological and psychological responses such as analgesia (pain reduction), sedation, euphoria, reduced breathing (respiratory depression), drowsiness, constricted pupils, and nausea. The physiological and psychological effects differ depending on the particular opioid and the type of receptor that is activated or inhibited.

3.3.1 Opioid Receptors

Opioid receptors are located in various locations of the brain that are implicated in the control of breathing and respiration, euphoria and pain control (Brunton, Buxton, & Parker, 2008; Eddy, Howes, & Arbor, 1935). They are also located in peripheral regions such as the intestinal tract (Brunton et al., 2008), and in areas relating to respiratory feedback drive, for example in the carotid bodies and the vagi (Pattinson, 2008) (further details in part 2 of this chapter).

There are three main groups of opioid receptors: mu (μ), delta (δ) and kappa (κ). All three produce analgesia when activated, but differ in other effects (Brunton et al., 2008). The mu-opioid receptor is the most widespread opioid receptor in the body and the primary target for a great variety of therapeutic drugs. However, mu-opioid receptors can also produce undesirable effects such as respiratory depression and constipation (Pasternak, 2006). The group of mu-opioid receptor agonists includes heroin, morphine, oxymorphone, methadone and fentanyl. The effect of other opioid receptors on respiration is less well understood. The delta-opioid receptors appear to have some inhibitory action on respiration and kappa-opioid receptors have little or no effect on respiration (Shook et al., 1990).

3.3.2 Heroin Pharmacology

Heroin is regarded as a powerful opioid. In its pharmacologically purest form it is more powerful than morphine weight for weight. If consumed orally, it crosses from the gastrointestinal tract to enter the blood and then undergoes metabolism in the liver, with a considerable proportion becoming deactivated (Way, Kemp, Young, & Grassetti, 1960). However, if injected intramuscularly or intravenously, it enters straight into the bloodstream and crosses the blood brain barrier (BBB), a cellular system that exists to protect the brain from potentially toxic molecules. The effect of heroin peaks within 20 seconds of an intravenous injection, and slightly later following intramuscular administration (Electronic Medicines Compendium (eMC), 2013; Klous, Van den Brink, Van Ree, & Beijnen, 2005). Heroin rapidly crosses the BBB but is also rapidly broken down into the active metabolites morphine, morphine glucuronide and 6-monoacetylmorphine (6-MAM) (Inturrisi et al., 1983). Heroin could therefore be considered not only as a drug in its own right but also as a pro-drug[5] for morphine (Sawynok, 1986). A key feature of heroin is that its chemical structure allows it to cross the BBB more easily than most other opioids. As a result, heroin has a very fast onset of action for brain effects and associated euphoric effect, which contributes to its high potential for addiction relative to other opioids.

Heroin is a strong agonist for opioid receptors, with particular affinity for the mu-opioid receptor: the heroin metabolite occupies the receptor until it loses its ability to bind. Figure 3-1 demonstrates the binding fit of a heroin metabolite (or any other opioid agonist) onto an opioid receptor.

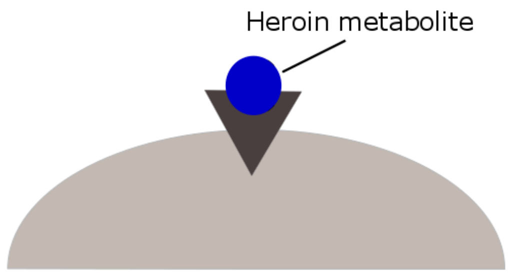

Figure 3-1: illustration of the heroin or metabolite (blue) attaching to an opioid receptor (grey triangle). This simplified illustration represents the metabolites of heroin, 3-monoacetylmorphine, 6-monoacetylmorphine and morphine (McDonald & Strang, 2016).

3.3.3 Other Opioids

Opioids differ greatly in their duration of action, and this is influenced by their elimination half-life, i.e. the amount of time it takes for half of the drug to be eliminated from the body. The

[5] A pro-drug is an inactive substance that becomes active in the body by a metabolic conversion process (Merriam-Webster, 2018)

half-life of a drug does not necessarily equate to its peak effects or its concentration at the relevant receptors, and in fact all drugs will continue to produce some effects after the stated half-life duration. Table 3-1 summarises some of the more commonly used opioids and their approximate half-life.

Table 3-1: Opioids along with their respective half-life approximations (Pasternak, 2006).

Drugs	**Approximate Half-life**
Heroin (Diamorphine)	6 minutes
Morphine	120 minutes
Hydromorphone	150 minutes
Oxymorphone	150 minutes
Codeine	180 minutes
Fentanyl	220 minutes
Tramadol (immediate release)	6 hours
Methadone	24 hours
Buprenorphine	37 hours

3.3.4 Heroin/Opioid Metabolism

Heroin breaks down into 6-monoacetylmorphine (6-MAM) and then into morphine, and thus, heroin as a drug lasts for much longer than the figure stated in the table above. There are two mechanisms by which opioids are metabolised in the liver: (1) via the enzymes known as the cytochrome P450 system[6], and (2) via other types of reactions, most commonly by a reaction known as glucuronidation[7]. Some opioids (e.g. methadone, tramadol and fentanyl) undergo only the former process and some (e.g. heroin and morphine) only undergo the latter process. If taken orally, heroin undergoes extensive metabolism as it enters the liver and consequently does not reach the systemic circulation. In this instance, heroin is largely converted to morphine before it reaches the general circulation (and hence before it reaches the brain). Heroin absorbed by the gastrointestinal tract travels directly to the liver where this conversion occurs (known as hepatic first-pass metabolism). Consumption through the intranasal, inhalatory, intramuscular and intravenous routes bypasses this initial stage in the liver, and

[6] This is one of two systems of enzymes (the other, less significant, group is known as UGTs (UDP-glucuronosyltransferases) involved in the breakdown of opioids and has gained great attention since we have developed a stronger understanding of the genetic influences on the effectiveness of the breakdown pathway (Holmquist, 2009).

[7] Glucuronidation is a general process that occurs in the breakdown of chemicals, mainly in the liver.

therefore produces more prominent brain effects compared to the oral route (Brunton, 2008; Smith, 2009).

3.3.5 Toxicological Analysis of Fatal Heroin Overdose Deaths

Toxicological advances mean that post-mortem examinations of fatal overdose cases are potentially able to give us a greater insight into the precarious stages before death. There are many studies examining the (often perplexing) discoveries, of metabolites of heroin found post-mortem. In some cases, these metabolites are lower than one would expect, suggesting that the term ‘heroin overdose’ is in itself is a misnomer (see section 3.5.2 on Unknown Purity for further details on this), Notwithstanding, with regards to novel research into post-mortem examinations, one study in particular stands out. Darke et al. (2016) analysed heroin metabolite concentrations to establish this as a proxy for survival times and estimated survival times in heroin-related mortality cases. Heroin is known to ‘deacetylate’ to 6-MAM within an average of 3 minutes after administration. Darke et al. found that the presence of the metabolite 6-MAM in post-mortem examinations could be used to distinguish between overdose cases that had survival times above 20-30 minutes subsequent to heroin administration and overdose cases below this time. The slight majority of cases (57%) were 6-MAM-absent and such the survival would have been at least 20-30 minutes. A large proportion of cases (43%) were 6-MAM-present meaning that the survival time would have been less than 20-30 minutes. Amongst these cases, a quarter had experienced bronchopneumonia (inflammation of the lungs) and authors reported that these cases were significantly more likely to test 6-MAM-negative, suggesting that survival time was over 20-30 minutes, an insidious overdose situation (description of overdose typology is in section 1.3 of this chapter) (Darke & Duflou, 2016). Whilst this piece of work is yet to be replicated, it is a promising indication of the factors that play a role in overdose deaths (Tas & McDonald, 2016).

3.4 Typology of Overdose Deaths

As described in Chapter 1, there is often disparity regarding definitions of drug-related deaths. Here, an overview of definitions related to overdose specifically is described. Whilst there is a clear understanding that overdose is a serious public health problem, and that opioids have a negative impact on the respiratory system, an accurate monitoring of overdoses requires reliable definitions, categorisations and technological advances.

The EMCDDA (2010) defines drug-related death as a death:

> […] directly due to use of illegal substances, although these often occur in combination with other substances, such as alcohol or psychoactive medicines. These deaths occur generally shortly after the consumption of the substance and are therefore considered 'directly caused by drugs'. (EMCDDA, 2010)

According to the ONS in the UK, a similar definition of drug-related deaths is as follows:

> Death where underlying cause is drug abuse or drug dependence and deaths where underlying cause is drug poisoning and where a substance controlled under the Misuse of Drugs Act 1971 was mentioned on the death certificate (Christophersen, Rooney, & Kelly, 1998).

Drug-related deaths are also known as 'drug-induced deaths' (a term used in the USA and increasingly in the EU), as 'poisonings' (which corresponds to the terminology used in the International Classification of Diseases) or in more common language as 'overdoses'.

3.4.1 What is an Overdose Death?

Overdoses are generally considered to be either accidental or with clear suicidal intent. However, the vast majority of overdoses in the drug misusing population are in the category of accidental drug overdoses (Farrell, Neeleman, Griffiths, & Strang, 1996). It is considered that some overdose deaths may fall into an overlap category where there is an absence of suicidal intent but nonetheless an overt lack of regard to personal safety (Vingoe et al., 1999).

Overdoses themselves can further be categorised into sudden- and slow-onset cases. Sudden-onset (or catastrophic) overdoses, when the victim loses consciousness with the needle in situ, often occurs after intravenous heroin administration. Slow-onset (or insidious) overdose deaths occurs over a longer period of time; often the victim is thought to be sleeping, leading to friends/family being unable to recognise the danger. In reality with these cases, they are drifting into a coma and it is typically caused by longer-acting oral pharmaceutical opioids, e.g. oral methadone (McDonald & Strang, 2016). It is thought that instant death, or catastrophic overdose, occurs in around 15% of cases (Lenton & Hargreaves, 2000; Sporer, 1999).

3.4.2 Non-fatal Opioid Overdoses

Non-fatal overdoses, historically known as 'near-miss overdoses', are regarded as strong predictors of fatal overdose (Coffin et al., 2007; Linn Gjersing & Bretteville-Jensen, 2015; Stoove, Dietze, & Jolley, 2009). They are purported to occur in over half of opioid users but the overall figure per year is difficult to quantify as definitions of 'non-fatal' vary greatly (EMCDDA, 2010; Sporer, 2003). Darke et al. (2003) examined several longitudinal and self-reported studies that had investigated fatal and non-fatal overdoses and attempted to establish a ratio between these two events. Overall, they found that an average annual fatal overdose rate of 0.8% and a non-fatal rate of 25% amongst heroin users is a reasonable prediction (Darke, Ross, & Hall, 1996; Darke, Ross, Zador, & Sunjic, 2000). This relates to an approximation that 3% of overdose events result in death. This is validated by emergency services call-out rates, in that not all overdoses result in ambulance attendance. It was estimated that ambulance attendances were around 51% with 12 attendances to every one overdose death (Wagner et al., 2015).

3.5 Risk Factors of Fatal Overdose

There are many factors that contribute to the risk of overdose in general and to fatal overdose in particular. Non-fatal overdoses are more common than fatal but the risk factors for both are the same. Incorporating the diverse range of studies available, it is possible to outline a complex set of factors and indicators that are involved in every drug using session, adapted from previous reviews (Rome et al., 2008; Frisher et al., 2012) (Table 3-2).

Generally speaking, it is likely that the more that these risk factors are cumulatively present, the greater the likelihood that the overdose will be fatal (Frisher et al., 2012). However, it is important to note that:

> while significant risk factors for opioid overdose fatality are clearly recognised, the mechanism of death is still poorly understood (Warner-Smith et al., 2001,p.1121).

This is still applicable today. Demographic data are extensive and valuable but clinical data are required in certain areas.

Table 3-2: Risk factors of opioid overdose.

Risk Factor/Indicator	Reference(s)
Type of opioid/drug	(Bartu et al., 2004; Stenbacka et al., 2010)
Bioavailability, route of administration, injecting site	(Darke & Ross, 2000; Degenhardt et al., 2011; Stewart, Gossop, & Marsden, 2002; Darke, Ross & Kay, 2001)
Purity and dose	(Darke, Hall, Weatherburn, & Lind, 1999; Desmond, Maddux, & Trevino, 1978; McGregor, Darke, Ali, & Christie, 1998)
Concurrent use of other drugs, especially other depressants	(Dietze, Jolley, Fry, & Bammer, 2005; Gossop, Stewart, Treacy, & Marsden, 2002; Martyres, Clode, & Burns, 2004; Zador, Sunjic, & Darke, 1996)
Age and gender	(Bartu et al., 2004; Darke, Kaye, & Duflou, 2006; Warner-Smith et al., 2001)
Duration of use	(Brugal et al., 2005; Hser, Hoffman, Grella, & Anglin, 2001)
Tolerance due to: **- current status of individual, e.g. in treatment or just out of treatment**	(Bell & Zador, 2000; Buster, van Brussel, & van den Brink, 2002; Thiblin, Eksborg, Petersson, Fugelstad, & Rajs, 2004; Wolff, 2002)
- post-prison release	(Bird & Hutchinson, 2003; Darke, Williamson, Ross, & Teesson, 2005; Digiusto et al., 2004; A Fugelstad, Stenbacka, Leifman, Nylander, & Thiblin, 2007; Oliver & Keen, 2003; Stewart et al., 2002)
Genetic and metabolic differences	(Kosarac, Fox, & Collard, 2009)
Underlying pulmonary diseases & other physical health problems (e.g. cardiovascular, liver)	(Jolley, Bell, Rafferty, Moxham, & Strang, 2015b; Warner-Smith, Darke, & Day, 2002; Warner-Smith et al., 2001)
Recent life problems/psychological distress	DORIS study (Neale & Robertson, 2005; Stewart et al., 2002)
Experience of previous overdoses	(Tobin, Davey, & Latkin, 2005)
Contextual/environmental factors	(Gerevich, Bacskai, Farkas, & Danics, 2005; Siegel, Hinson, Krank, & McCully, 1982)
- using alone	- (Best et al., 2002; Dietze et al., 2002; Tracy et al., 2005)
- fear of potential police involvement	- (Pollini, McCall, Mehta, Vlahov, & Strathdee, 2006; Tobin et al., 2005)
- using outdoors (e.g. street injectors)	- (Anoro & Ilundain, 2003; L Gjersing et al., 2013; Hunt, 2006)
Lack of naloxone availability	(Baca & Grant, 2005; Strang, Darke, Hall, Farrell, & Ali, 1996; Strang, Grifiths, Powis, & Gossop, 1999)

3.5.1 Route of Administration and Relevant Risk of Overdose

A high bioavailability (the proportion of the actual drug that reaches the systemic bloodstream) usually equates to a higher rate of absorption and increased risk of overdose. Bioavailability is considerably affected by the route of administration, which determines what type of metabolism (breakdown) the drug undergoes, but also by the dose taken and the purity of the drug. The combination of the latter two factors will determine the total amount of active substance consumed.

In Table 3-3 below, routes of administration are listed in order of increasing risk of overdose, assuming that dose and purity are constant.

Table 3-3: Risk of overdose by route of administration (descending order) (McDonald & Strang, 2016)

Route	Description
1. Intravenous (injecting into vein)	Powder or crushed tablets prepared for injection usually using water and an acidifier (e.g. heroin, crushed pharmaceutical opiate drugs) which is typically self-administered (or given by fellow drug user) as a bolus, thus delivering full sudden onset of drug effect when the bolus of drug reaches and crosses the blood-brain barrier. By virtue of the instant delivery following the pushing of the syringe-plunger, there is no scope for reducing the dose if the effect of the heroin is greater than expected. Heroin through this route has 100% bioavailability.
2. Intramuscular (injecting into muscle)	This is similarly typically self-administered quickly but, by virtue of being injected into muscle (instead of into a vein), it is absorbed more slowly and so, even if eventually fully absorbed, it does not produce the same front-end bolus effect as intravenous use. As with intravenous use, there is no scope for reducing the dose if the effect of the heroin is greater than expected. Bioavailability is slightly lower than that of intravenous (Girardin, 2003).
3. Inhalation (smoking, 'chasing')	Vaporising heated heroin base (brown powder), usually on foil, is known as 'chasing the dragon'. By utilising the vast surface area of the lungs (as with cigarette smoking), 'chasing' produces rapid absorption and hence rapid brain effect. However, the technique of 'chasing' involves running the melted heroin up and down the heated tinfoil and inhaling the sublimate in the vapours – and this technique is not instant in the same way as pushing a syringe-plunger and, consequently, does not produce the rapid bolus effect. Hence inhalation results in an effect of slightly slower onset which thereby gives opportunity to reduce dose if the effect is larger than expected.
4. Intranasal (snorting)	Whilst not common, the white powder (salt) form of heroin occurs in some countries and communities. Snorting results in a mix of fairly rapid-onset as well as extended duration effect.

	Heroin bioavailability intranasally is approximately half of the intramuscular route (Cone, Dickerson, Paul, & Mitchell, 1993).
5. Oral	Ingesting orally any drug as a tablet/capsule/liquid (e.g. methadone, morphine sulphate (MST), dihydrocodeine) is likely to produce a slow-onset effect as it is gradually absorbed from the stomach or further down the alimentary tract. The extent to which it then produces effects on the brain varies greatly between the different opiate drugs, and is markedly affected not only by how comprehensively it is absorbed, but also, crucially, by the extent of first-pass metabolism. Thus, there is no opportunity to reduce dose if the effect is larger than expected, but there is also no sudden-onset bolus effect. Heroin has <35% bioavailability when taken orally (Rook et al., 2006)

3.5.2 Unknown Purity as a Risk Factor

Much of the relationship between, and relationship of, heroin purity and mortality rates in the UK has been described in Chapter 1. This section focusses on the concept of purity and dose as a risk factor for opioid overdose. The classical depiction of a fatal overdose is of that deriving from a quantity or quality of the drug in excess. In the 1970s, Desmond and colleagues were the first to comment on the 'pharmacologic overdose' hypothesis, which states that there is a correlation between potency and of frequency of heroin overdose deaths (Desmond et al., 1978). Their paper in 1978 focussed on deaths in Texas, USA over a 5-year period and the mean dose of heroin in street packages (ranging from 1mg to 196mg). There was a low, non-significant correlation between monthly average heroin dose (relevant to potency) and monthly number of overdose deaths during that time (Desmond et al., 1978).

This was following two studies in the USA which had found a positive correlation between heroin overdose deaths and the pharmacologic dose hypothesis (Garriott & Sturner, 1973; Greene et al., 1974). Since this time, the evidence supporting or disproving this correlation has been mixed (see Appendix B for a list of publications and the relative evidence).

This confounding evidence consistently contributes to simplistic media reports which inaccurately report on drug-related deaths. In many media reports deaths are linked to contaminated or 'killer' batches of heroin that are often embellished or simply false (Bammer, Ostini, & Sengoz, 1995; Darke et al., 1999). Interestingly, users who were interviewed after experiencing non-fatal overdoses believed that the main reasons were related to the quantity or strength of the heroin (Darke et al., 1996; McGregor et al., 1998).

It is true to state that 'street' heroin is subject to unpredictable variations in drug purity and may contain a variety of adulterants or contaminants mixed in, making it difficult for the user to determine the amount of active substance to use. However, the picture is far from clear cut, as large numbers of fatal overdose cases have low blood morphine concentrations, often below, or similar to, those of living intoxicated heroin users or of heroin users who died from other causes (Darke, Duflou, & Torok, 2010; Darke & Farrell, 2014; Davidson et al., 2003). Additional factors may have a stronger contribution to fatal cases (Table 3-2), e.g. the level of tolerance of the individual, consumption of other depressants, or organ (lung, liver) failure. In addition, an important point to consider is that harmful contaminants that may have contributed to the fatal outcome of the overdose may often not be detected in toxicological analyses of blood, drugs and used syringes (Darke et al., 2010).

The idea that purity plays a role in overdose is further challenged by the observation of overdoses in clinical settings as well as in an illicit drug market scenario, most strikingly in a heroin-assisted treatment clinic. Even where a pharmaceutical and titrated dose is administered, though rare, overdose events still occur (Oviedo-Joekes et al., 2009; Strang, Metrebian, et al., 2010).

To provide further context to this, in the UK, the Randomised Injectable Opiate Treatment Trial (RIOTT) compared supervised injectable heroin or injectable methadone versus oral methadone as treatment for chronic heroin addiction. Treatment was provided for 26 weeks and the rate of overdose (non-fatal) was reported to be around 1 in every 6,600 diamorphine injecting events (Strang, Metrebian, et al., 2010). These overdose events were immediately after injection, and in patients who had consecutively been taking the same daily, titrated dose. In a similar trial in Canada, the North American Opiate Medication Initiative (NAOMI) clinic saw a figure of around 1 per 8,300 injecting events (Oviedo-Joekes et al., 2009). In both of these large-scale trials, the events required an intervention of either oxygen or naloxone. In similar related work, the level of participants' regular dose of diamorphine showed significant changes in oxygen saturation (blood oxygen level) in half of all testing sessions (Dursteler-Mac Farland et al., 2000; Stoermer et al., 2003; Stohler et al., 1999; Mitchell et al., manuscript available on request).

In Australia, a recent study into the supervised injectable drug clinic, the Medically Supervised Injectable Centre (MSIC) in Sydney, examined a total of 2,860 opioid overdoses (either heroin or oxycodone) between 2007 and 2014. Approximately two-thirds of all opioid overdoses were heroin-related, 12.7 overdoses per 1000 injections. Severe overdose/respiratory depression was reported significantly more in the overdoses related to heroin compared to oxycodone. Interestingly, no differences were reported across the groups with regards to concurrent use of depressants, reduced level of tolerance or using a larger quantity than usual (Roxburgh, Darke, Salmon, Dobbins, & Jauncey, 2017). Clearly, overdoses can occur without variation in administered heroin doses.

3.5.3 Concurrent Use of Other Drugs

There is an increased risk of heroin/opioid overdose if alcohol and other sedative drugs (e.g. benzodiazepines) are also consumed (CDC, 2017). This 'cocktail' of drugs and alcohol contributes to a great number of the overdose deaths. In the presence of other central nervous system depressant drugs, a usually well-tolerated dose of heroin can prove fatal.

Polydrug use is possibly the most important risk factor in overdose deaths. A typical user is expected to have used at least ten different drugs in their lifetime, and at least six in one year (Darke, 2011) and higher levels of polydrug use appears to be associated with a higher risk of overdose, psychopathology and poor treatment outcome (Darke & Ross, 1997; DeMaria et al., 2000).

Alcohol and benzodiazepines are the most commonly co-administered drugs. Alcohol is present in over half (Darke et al., 2000; Fugelstad et al., 2003; Ruttenber et al., 1990), and benzodiazepines in a quarter of fatal opioid overdose cases (Darke et al., 2010; Davidson et al., 2003; Fugelstad et al., 2003). In two prominent longitudinal studies, the National Treatment

Outcome Research Study (NTORS) and the Drug Outcome Research in Scotland Study (DORIS), benzodiazepines were considered one of two major risk factors (the other being injecting route of administration) (Neale & Robertson 2005; Stewart et al., 2002). In another study, benzodiazepine use was shown to have increased the risk of overdose 28 fold (Dietze et al., 2005).

Benzodiazepines are a class of drugs used for their anxiolytic, sedative and anticonvulsant properties. Benzodiazepines, like alcohol, represent a desirable combination for the heroin user. They are extensively abused by individuals in treatment for their addiction problems (Strang et al.,1994). In any one month, a third to half of heroin users will also use a benzodiazepine, for both clinically prescribed and recreational purposes, with quicker onset versions being preferred (e.g. diazepam and alprazolam) (Bargagli et al., 2006; DeMaria et al., 2000).

Whilst most of the longitudinal, qualitative and observational studies discussed thus far show a great connection between the two drug groups, the direct pharmacological and physiological evidence is somewhat limited, particularly for the drug of greatest concern, heroin. In terms of the physiological effects, benzodiazepines have been shown to decrease oxygen saturation significantly in the presence of opioid substitution drugs such as methadone and buprenorphine (Lintzeris et al., 2007, 2006). Furthermore, according to Darke, co-administration of a depressant greatly increases the likelihood of a fatal situation because it potentiates the respiratory depressant effects of heroin. In the presence of depressants, a normal dose of heroin may be fatal (Darke, 2011). However, whether this apparent increased risk of respiratory depression occurs via a potentiation of opioid effects or a synergistic action of more than one depressant is not well understood.

3.5.4 Gender and Age

It is understood that there is an increased vulnerability amongst older opioid users (Gao et al., 2016; Pierce, Millar, Robertson, & Bird, 2018) and age is a risk factor for opioid overdose (Bartu et al., 2004; Warner-Smith et al., 2001). The basis of this is most likely related to the length of time that individuals have been taking illicit drugs rather than chronological age

(Bartu et al., 2004; Hall, Degenhardt, & Lynskey, 1999; Langendam, van Brussel, Coutinho, & van Ameijden, 2001). A history of overdose is thought to increase the prevalence of high-risk behaviours and most fatalities are thought to have had a number of overdoses prior to the fatal overdose (Warner-Smith et al., 2001). Therefore, it may be that increasing age is a marker for increasing overdose experience and consequent risk of fatal overdose.

Males are consistently more likely to experience an overdose than females (Chen, Kuo, & Tsai, 2001; Gossop et al., 2002; Hall et al., 1999) and have even been shown to have a greater hazard of all-cause death compared to females (Bartu et al., 2004).

3.5.5 Lung Disease and Overdose Mortality

Warner-Smith et al., in their review of the causes and complications of overdose deaths stated that there was

> Biological plausibility of an association between pulmonary dysfunction and overdose mortality and the potential for substantial rates of pulmonary dysfunction among heroin users suggests that pulmonary morbidity may contribute to mortality from opioid overdose. (Warner-Smith et al., 2001, p.8).

Seventeen years later, unfortunately, there is still very little experimental evidence that has investigated this link. Much of the literature on overdose risk in drug users is focused on injecting drug users and blood borne viruses such as HIV and infectious diseases. In the 1990s there was a gradual trend towards smoking heroin (Smyth, O'Brien, & Barry, 2000; Strang, Griffiths, & Gossop, 1997). This was, in part, due to smoking (or inhaling) being perceived as 'safer'. Currently, in the UK, smoking is still the more common form of administering heroin. Respiratory clinicians and researchers have increasingly been noting airways disease due to the effects of opioid smoking (Burhan et al., 2018; Lewis-Burke, Vlies, Wooding, Davies, & Walker, 2016; Palmer et al., 2012; Walker, Thwaite, Curtis, & Calverley, 2015; Yadavilli et al., 2014). These studies have shown that there is a high prevalence of chronic lung diseases and significantly more drug users are diagnosed with lung diseases than controls. However, despite the few studies that have investigated obstructive lung disease in heroin smokers ('chasers') (Buster, Rook, Van Brussel, Van Ree, & Van den Brink, 2002; Jolley, Bell, Rafferty, Moxham, & Strang, 2015a; Walker et al., 2015; Yadavilli et al., 2014), very little is actually known of the link between heroin administration and lung disease, let alone the relationship with overdose risk. There is clearly an important link between these areas that requires investigation. The second part of this chapter will describe respiratory physiology in relation to lung disease in greater depth.

3.5.6 Environmental

Another factor that is thought to influence vulnerability to overdose is related to situation-specific tolerance. This is based on work by Siegel et al. in the 1980s. In studies of rat models where morphine was administered, there appeared to be increased overdose signs in a differing environment to that which the effects originally took place/to where they had been accustomed to taking it. Rats that were given morphine in the same circumstances, on the other hand, had a smaller effect as if they had been ‘expecting’ its effect (Siegel, Hinson, Krank, & McCully, 1982). Siegel also interviewed heroin overdose survivors, and most had administered in an environment not previously associated with drug use (Siegel, 1984). Furthermore, O’Brien et al. showed that the anticipation and preparation in taking the drug appeared to act as a conditioned stimulus, reducing the action of the drug and contributing to the development of a corresponding tolerance (O’Brien, Childress, McLellan, & Ehrman, 1992a, 1992b). This was seen in a study on the physiological effects of Hydromorphon dosing on differing occasions where participants were either give the opiate without prior indication or where they self-administered the opiate (O’Brien et al., 1992a).

It is important to note that the issue of suicide as a risk factor is not discussed in this thesis. It is understood that there is a 14 times greater risk of suicide among heroin users than the general population (Harris & Barraclough, 1998; Wilcox, Conner, & Caine, 2004). It is likely that someone with a history of attempted suicide is more at risk of overdose due to an indifference of whether they ‘live or die’, but this is a complex phenomenon with different factors, and thus, is beyond the scope of this thesis.

Part 2: The Impact of Opioids on Breathing Mechanisms

To understand why heroin and other opioids are particularly dangerous, it is important to consider the fundamentals of breathing and lung physiology. This section will describe respiratory physiology provided in the subsequent part.

3.6 Introduction to Respiration

The lungs function to continually exchange oxygen and carbon dioxide with the external environment in order to maintain low concentrations of carbon dioxide and high concentrations of oxygen in the tissues of the body (Levitzky, 2013). Normal resting breathing is driven by the respiratory centres of the brain located in the medulla and pons regions of the brainstem. Sensors, also known as peripheral and central chemoreceptors (e.g. the carotid body) of the body and brain provide a precise self-regulating system. These receptors are sensitive to changes in arterial blood partial pressures of oxygen, carbon dioxide and acid-base status. The respiratory centres monitor the feedback from the peripheral sensors and send the appropriate stimuli to initiate pulmonary ventilation (breathing) (Figure 3-2).

A build-up of carbon dioxide in the blood, and critically low oxygen levels are toxic. If not adequately expelled via the lungs, an accumulation of carbon dioxide can lead to the condition known as hypercapnia. This in turn causes a decrease in blood pH (known as acidosis, the accumulation of acid substances in the body) and is typically accompanied by a decrease in blood oxygen (hypoxaemia) and finally hypoxia (a condition in which oxygen is deprived from the tissue in a region of the body or the whole body). If this state of low oxygen and high carbon dioxide in the blood is prolonged for a period of time, or if it is rapid and profound, it is usually fatal (Levitzky, 2013).

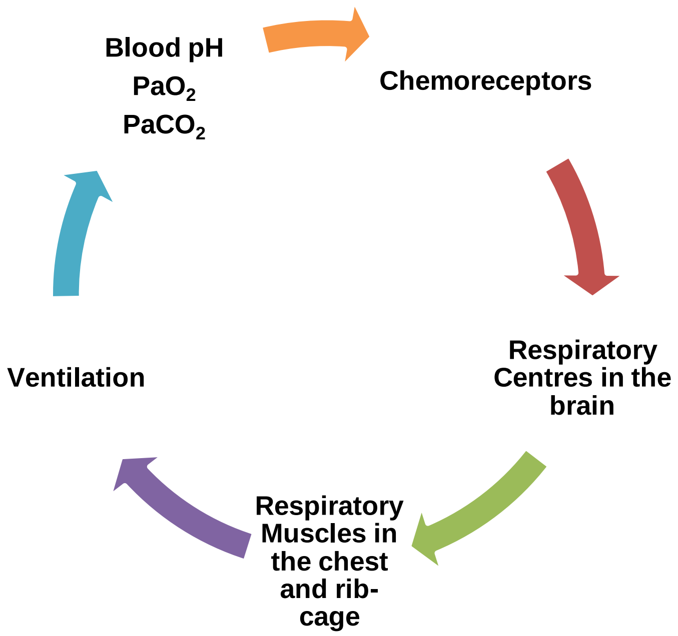

Figure 3-2: Respiratory Feedback Loop. PaO_2: partial pressure of oxygen in arterial blood; $PaCO_2$: partial pressure of carbon dioxide in arterial blood.

3.6.1 Initiation of a Breath in Healthy Respiratory Function

Initiation of respiratory muscles arise from the central brainstem region (medulla and pons) via spinal and cranial motor neurons (more details in Section 3.8). Respiratory muscles act to move air in and out of the lungs through their actions on the ribcage and are conventionally described as being inspiratory or expiratory. Inspiratory muscle contraction expands thoracic cavity (the space inside the ribcage), leading to a fall in the pressure between the thin fluid-filled surrounding layers of the lungs (intrapleural pressure). The resulting pressure gradient across the lung and pleural space causes lung expansion, resulting in a fall in pressure in the airways and alveoli (airway pressure). Inspiratory flow begins when the airway pressure falls below atmospheric pressure. Expiration is passive in healthy individuals breathing at rest. Expiratory muscles are recruited when ventilatory demands increase, for example, during exercise.

3.7 Respiratory Physiology: Structure & Function

3.7.1 Definitions

Table 3-4: Table of definitions in relation to respiratory physiology.

Term	Definition
Afferent nerve fibre	Carries impulses towards the central nervous system
Efferent nerve fibre	Carries impulses away from the central nervous system
Tonic drive	Tonic input adapts very slowly to a stimulus, in comparison to phasic input which responds very rapidly. Tonic inputs continue to produce action potentials over the time of the stimulus. It is often characterised by a steady state of action potential firing at a constant frequency.
Phasic firing	Occurs after a neuron is activated, it is usually restricted to one, a few or a short burst of action potentials and will often rapidly return to the resting state.
Alveolar ventilation	The exchange of gas between the alveoli and the external environment
Ventilatory frequency or respiratory rate	The number of breaths taken per minute. Normal adult respiratory rate is between 12 and 20 breaths per minute.
Minute ventilation/ minute volume	Volume of gas inhaled or exhaled from the lungs per minute.
Tidal volume	Normal volume of air inhaled or exhaled when extra effort is not applied.
Smooth muscle	Muscle tissue that contracts without voluntary control, having fine myofibrils but lacking transverse striations and found in the walls of internal organs, blood vessels and hair follicles.
Skeletal muscle	A form of striated muscle tissue which is under the voluntary control of the somatic nervous system. Most skeletal msucles are attached to bones by tendons.
pO_2	Partial pressure of oxygen
PaO_2	pO_2 in arterial blood
pCO_2	Partial pressure of carbon dioxide
$PaCO_2$	pCO_2 in arterial blood

3.7.2 Structural Anatomy of the Respiratory System

The lungs are a pair of organs within the thoracic cage whose principal function is gas exchange. Atmospheric oxygen diffuses passively from the alveoli into the pulmonary capillary blood, down a partial pressure gradient. Carbon dioxide diffuses from the pulmonary capillary blood into the alveoli and is thereafter expelled into the atmosphere. The thoracic cage consists of the sternum and 12 pairs of ribs. The ribs slope inwards (inferiorly) and backwards (anteriorly) from the vertebrae. A combination of their sloping orientation with their elevation allows the ribcage move up and out (known as a ‘pump and bucket-handle motion’) (Hamid, Qutayba; Shannon, Joanne; James, 2005).

The lungs are surrounded by serous membrane (visceral pleura) which folds in on itself to form a two-layer structure (Gray, 1918). The outer membrane (parietal pleura) is attached to the inside of the rib cage. The two pleural membranes are maintained close together (but do not touch) due to reciprocal repulsive forces and the existence of surface tension from the fluid present between the membranes, which opposes the elastic recoil of the parenchyma (functional parts of the organ) and prevents lung collapse (Hamid, Qutayba; Shannon, Joanne; James, 2005).

3.7.3 Respiratory Muscles

As previously described, pulmonary ventilation requires volume change of the lungs, which occurs as a result of contraction of the respiratory muscles (Ratnovsky, Elad, & Halpern, 2008). The respiratory muscles work together to increase thoracic volume, expand the rib cage, to lower pleural and intrapulmonary pressures and cause air to flow into the lungs (Figure 3-3). Adequate gas exchange is maintained by appropriate functioning of the respiratory muscle pump which consists of inspiratory and expiratory muscles. The inspiratory muscles include the diaphragm and external and parasternal intercostal muscles as well as accessory muscles of the upper chest and neck. Expiratory muscles are the internal intercostal muscles and abdominal muscles.

The diaphragm is the principal inspiratory (and skeletal) muscle and is involved in 70-80% of the work required for breathing in healthy individuals (Moxham & Jolley, 2009). The diaphragm is positioned at the interface of the thoracic and abdominal cavities and is innervated by the phrenic nerves. During contraction of the diaphragm, the muscular sheet flattens, compresses the abdominal region and causes the volume of the thoracic cavity to increase (Hamid, Qutayba; Shannon, Joanne; James, 2005). This increases intra-abdominal pressure and causes an outward movement of the lower part of the ribcage. The diaphragmatic muscle fibres are slow twitch, resistant to fatigue, oxidative fibres (De Troyer, Legrand, & Wilson, 1996) (type 1 fibres, Table 5).

Intercostal muscles consist of two thin layers of intercostal muscles each occupying the intercostal interspace. The outer layer (external intercostals) and the inner layer (internal intercostals) have fibre orientations that are perpendicular to one another (De Troyer & Estenne, 1988). Both sets of intercostal muscles are innervated by the intercostal nerve and play an important role in respiratory function (De Troyer, 2005; Taylor, 1960). The internal intercostal muscles having a greater role in expiration, contracting to collapse the rib cage, whereas the external intercostals acting to raise the lower part of the rib, leading to an inspiratory effect. Between the sternum and costo-chondral junction (the joint between rib and costal cartilage on the front of the rib cage), the first five interspaces are replaced by flat broad tendons (fibrous aponeuroses), and the internal intercostals in these interspaces are known as parasternal intercostal muscles (Figure 3-3) (Han, Gayan-Ramirez, Dekhuijzen, & Decramer, 1993).

The parasternal intercostal muscles are similar to internal intercostal muscles anatomically but not functionally. The parasternal intercostal muscles have a role in inspiration and are termed the ‘inspiratory intercostals’. These muscles are slow twitch and resistant to fatigue (De Troyer et al., 1996), similar to diaphragmatic muscle (Table 3-5). Contraction of the parasternal intercostal muscles increases specific regions of the chest wall (the lateral and anteroposterior diameters) (De Troyer, Kelly, Macklem, & Zin, 1985). There are many animal studies that have investigated the role of this group of muscles. Denervation of these muscles in anaesthetised dogs led to decreased tidal volume, minute ventilation and increases in partial pressure of carbon dioxide (pCO_2) (De Troyer & Yuehua, 1994; Sugimori, Kochi, Nishino, Shinozuka, & Mizuguchi, 1993). Selective denervation of the chest wall in dogs showed that the parasternal intercostal muscles were responsible for around 80% of rib motion during resting breathing (De Troyer, 1991).

Examining the changes to the intercostal muscle length using computed tomography (CT) scanning and cadaveric studies have shown that the parasternal intercostal muscles shorten during passive lung inflation, and it is said that these muscles have an inspiratory mechanical advantage, albeit less than that of the external intercostal muscles (De Troyer, Legrand, Gevenois, & Wilson, 1998; Wilson, Legrand, Gevenois, & De Troyer, 2001). Essentially, the mechanical advantage of parasternal intercostal muscles in humans is four-fold greater in the second interchondral space compared to the fifth interchondral space (De Troyer et al., 1998)

(Figure 3-3). This is relevant to measures of respiratory depression described further on in this chapter.

Studies investigating activation of these muscles in isolation show that they do affect ribcage motion and volume change of the thoracic cavity, but their role in the fully intact system is dependent on their interaction with other muscle groups as well, in particular the external intercostal muscles and diaphragm (Decramer & De Troyer, 1984). Parasternal intercostal muscles act together with the diaphragm and they are consistently active during inspiration (only becoming inactive when the inspired volume is minimal) (Butler & Gandevia, 2008; De Troyer & Sampson, 1982; Easton et al., 2010; Gandevia, Leeper, McKenzie, & De Troyer, 1996; Gandevia, Hudson, Gorman, Butler, & De Troyer, 2006).

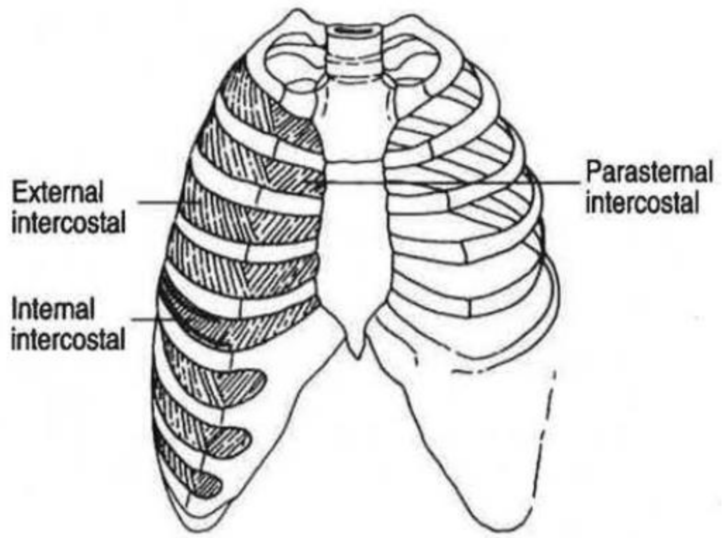

Figure 3-3: illustration of the location of intercostal muscles (Han et al., 1993).

3.7.4 Respiratory Muscle Contraction and Physiology

Respiratory muscles consist of skeletal muscle fibres, nerves and blood vessels bound together by connective tissue. A unit of a skeletal muscle is a single motor unit (motor neuron) and the group of muscle fibres that the neuron supplies. The neuronal cell bodies are located in the spinal cord. Muscle fibres themselves contain thread-like myofibrils that exist across the length of the muscle fibre. Mitochondria and a structure that stores calcium (sarcoplasmic reticulum) are also important components of muscle contraction. The outer cellular membrane enveloping the fibre (sarcolemma) consist of tubular projections (transverse t-tubules) that project into the fibre, to the sarcoplasmic reticulum. They are defined by their functional properties; slow-twitch (type 1) or fast-twitch (type 2). Myosin is a protein that converts chemical energy into mechanical energy. Different forms of myosin are expressed in human skeletal muscle, and there are also various muscle fibre types which impact their function in the respiratory system. Table 3-5 represents the characteristics of different muscle fibre types.

Table 3-5: Classification of muscle fibres (Scott, Stevens & Binder–Macleod, 2001)

Characteristics	**Type I**	**Type IIA**	**Type IIX**
Contraction Time	Slow	Fast	Very Fast
Oxidative Capacity	High	High	Low
Diameter	Small	Medium	Large
Resistance to Fatigue	High	Moderate	Small
Generating Force	Small	Moderate	Very High

3.7.5 Electrical activation of muscles

An action potential that arises in the motor neurone supplies the motor unit and leads to a release of acetylcholine into the neuromuscular junction. Acetylcholine binds to its receptors allowing sodium ions to enter the cell and causing a depolarising excitatory postsynaptic potential that is above threshold and triggers an action potential. This travels along the sarcolemma and through the t-tubules, resulting in release of calcium ions from the sarcoplasmic reticulum (Tortora & Grabowski, 2000; Widmaier, Raff, & Strang, 2013) (Figure 3-4). The number of active cross-bridges (i.e. the tension in the muscle) is a function of the calcium ion concentration. Each excitation of the muscle cell leads to an increase in intracellular calcium ion that is sufficient to bind all the regulatory protein complexes involved in contraction (troponin-tropomyosin), allowing the head of the myosin filament to attach to the actin filament (microfilament structure consisting of actin protein molecules within the cytoskeleton). A ‘power stroke’ follows whereby a new molecule of energy (adenosine triphosphate; ATP) is formed and binds to myosin releasing it from its attachment. The repeated actions of many actin-myosin complexes result in shortening of the sarcomere which produces either a contraction of the muscle or generation of tension depending on whether the ends of the muscle are fixed.

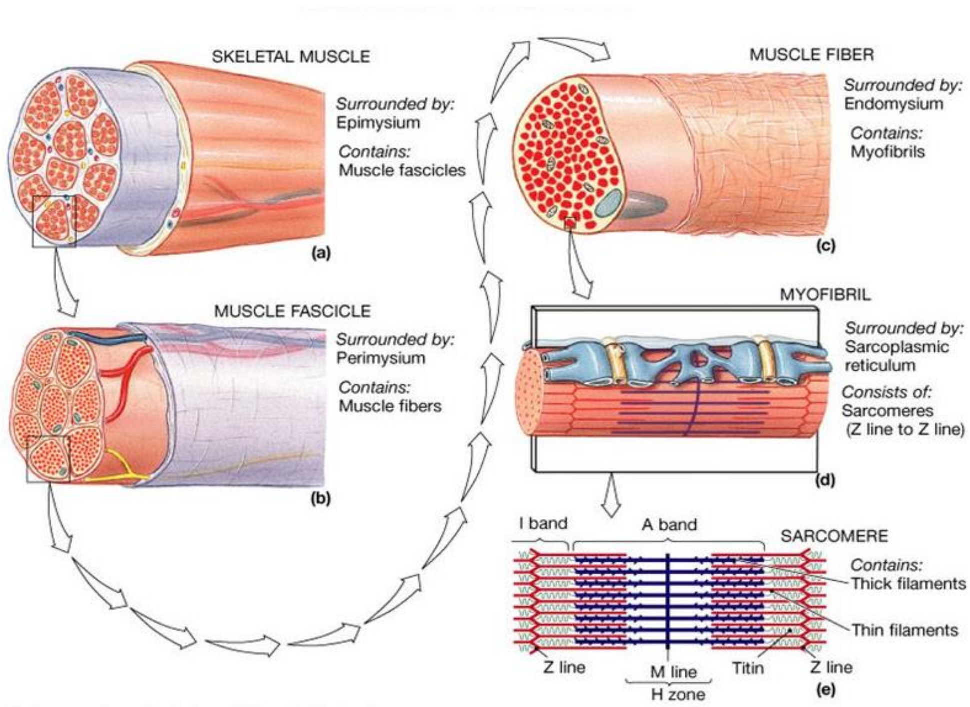

Figure 3-4: Diagrams of skeletal muscle, muscle fibre, myofibril to sarcomere (Marieb & Hoehn, 2013).

3.7.6 Factors Affecting Muscle Contraction

The force generated within a muscle during a contraction depends on the length of the muscle at the point of stimulation, the number of muscle fibres that are stimulated, the velocity of muscle fibre shortening and the frequency at which the fibres are stimulated. These are all closely related and rarely occur in isolation. This length-tension relationship is a product of the degree of overlap of the actin and myosin filaments.

3.7.7 Load-Capacity Balance of the Respiratory Muscles

The action of any muscle is dependent on the imposed load as well as its capacity (Ratnovsky et al., 2008). During resting breathing, the load on healthy human respiratory muscles is small. However, the variety of different pathophysiological changes that occur in lung disease can significantly alter the balance between the load imposed on the respiratory muscles and their capacity. In obstructive lung disease, there is an issue of increased airways resistance, hyperinflation and intrinsic positive end-expiratory pressure (PEEP)[8] that place an additional load on the respiratory muscles. In addition to these, in emphysema (a type of chronic lung

[8] Intrinsic PEEP is a positive pressure in the airways at the end of expiration, or put simply, an 'incomplete expiration' prior to the initiation of the subsequent breath

disease; discussed further in Part 3), the diaphragm is flattened and fibres become shortened. The diaphragm is less able to generate tension, such that the metabolic requirements are greater for a given workload (Byrd & Hyatt, 1968). Thus, the actual neural input to respiratory muscles has to increase to compensate for this change in load-capacity balance and to maintain adequate levels of ventilation for blood gas homeostasis.

3.8 Control of Respiration and Respiratory Drive

The drive to respiration, or neural respiratory drive, is generated by the respiratory centres in the brainstem, specifically the medulla and pons (Feldman & Del Negro, 2006; Lumsden, 1923; Pattinson, 2008). It is modulated by inputs from the cortex (Janczewski & Feldman, 2006; McKay, Evans, Frackowiak, & Corfield, 2003) as well as central (brainstem) and peripheral (carotid and aortic bodies) chemoreceptors (Bruce & Cherniack, 1987; Richerson, 2004) that sense changes in the blood. The respiratory centres act to control ventilation in order to maintain blood gas homeostasis.

3.8.1 Respiratory Rhythm

Rhythmic patterns and breathing movements are generated by the medullary and pontine respiratory networks which produce inspiratory and expiratory actions via spinal and cranial motor neurons to relevant respiratory muscles. A motor neuron has a cell body within the spinal cord, and an axon that projects out to organs or glands. The respiratory motor patterns are controlled by inputs within medullary neurons which exist as interconnected bilateral columns (Figure 3-5).

Lumsden et al.'s work on decerebrate cats was seminal in establishing that the brainstem was essential for respiration (Lumsden, 1923). They showed that transections at varying levels of the pons and medulla produced differing effects on the respiratory rhythm. The majority of respiratory neurones are concentrated into four nuclei: 1) the dorsal respiratory group (DRG) within the nucleus tractus solitarius (NTS); 2) the ventral respiratory group (VRG), which contains the nucleus ambigualis (NA) and the nucleus retroambigualis (NRA); 3) the pre-Bötzinger complex; and 4) the Bötzinger complex, located in and near the nucleus retrofacialis.

The pre-Bötzinger complex in the ventro-lateral region of the medulla is a small area that can produce a respiratory rhythm in isolation, *in vitro* (Rekling & Feldman, 1998; Smith et al., 2000; Smith, Ellenberger, Ballanyi, Richter, & Feldman, 1991). However, whilst this has been confirmed in rodents, it has not been identified in humans. The pre-Bötzinger complex was thought to be a pacemaker for respiratory rhythm but emerging evidence shows that it works with another group of nuclei called the Retro-trapezoid/parafacial respiratory group (RTN/pFRG) (Janczewski & Feldman, 2006; Onimaru & Homma, 2003) in oscillation. These coupled networks are strongly modulated by the pons (Smith, Abdala, Koizumi, Rybak, & Paton, 2007) specifically the Kölliker-Fuse nucleus, the parabrachial complex and the locus coeruleus (Figure 3-5).

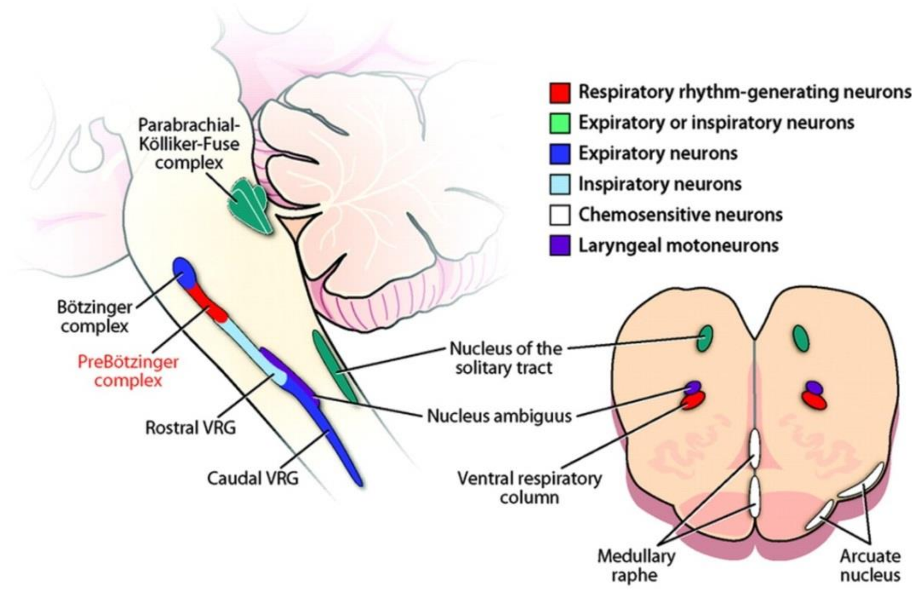

Figure 3-5: illustration of the nuclei involved in respiratory control (Benarroch, 2007).

The Bötzinger complex is composed of expiratory neurones as well vagal and glossopharyngeal motor neurones (Taveira da Silva et al., 1983) (10^{th} and 9^{th} cranial nerves respectively). The NTS is the primary site that receives lung and peripheral chemoreceptor afferent input. The DRG consists only of inspiratory neurones which act immediately prior to the onset of inspiration and relay the activity to the phrenic nerves (involved in innervating the diaphragm) (Dobbins & Feldman, 1994). This activity lasts for around two seconds in adults and subsequently ceases to allow for passive expiration (Hamid, Qutayba; Shannon, Joanne; James, 2005). The DRG is responsive to differing afferents from the chemoreceptors and lung mechanoreceptors via cranial nerves and spinal cord, and also from descending afferents from higher brain regions. The DRG inspiratory neurones inhibit expiratory neurons of the VRG and pontine respiratory group (PRG) (Alheid & McCrimmon, 2008).

The NA of the VRG contains premotor inspiratory neurones that supply the external and parasternal intercostals and accessory muscles of inspiration and the laryngeal motor neurones (Subramanian & Holstege, 2009), and the parasympathetic input to the heart and bronchioles (Purves et al., 2001). The PRG counteracts the influence of the medullary respiratory centres. In studies that have examined the respiratory effects without any influence of the PRG have observed a slow, rhythmic, gasping breathing pattern (Wang, Ngai, & Frumin, 1957). The PRG consists of a mix between expiratory neurones (in the medial parabrachial nucleus) and inspiratory neurones (in the lateral parabrachial nucleus and Kölliker-Fuse nucleus).

In relation to cortical control, volitional control of breathing is influenced by descending input from the cerebral cortex to the medullary respiratory centres. Voluntary control bypasses the medullary and pontine respiratory centres and interacts with spinal respiratory motor neurones (Tortora & Grabowski, 2000).

3.8.2 Respiratory Chemoreceptors and the Feedback Loops Which Control Breathing

As briefly discussed previously in this chapter, chemoreceptors respond to changes in pH, pO_2 and pCO_2 in the blood. There are differences in how responses to these changes occur, and how sensitive the chemoreceptors are to each of these. Minor increases in pCO_2 lead to significant and rapid changes in ventilation (Nattie, 1999), and contrastingly, decreasing pO_2 is hyperbolic in that large changes in pO_2 are required to mediate a change in ventilation at first, but the increase in ventilation thereafter is rapid (Powell, Milsom, & Mitchell, 1998).

Central chemoreceptors sense changes in pH, providing a tonic drive to the respiratory motor output. It is now understood that there are multiple chemo-sensing areas in the lower brain region, mainly in the brainstem, whereas classically it was thought that there were only three. These include the NTS, midline medullary raphe, pre-Bötzinger complex, and the RTN/pFRG in the medulla and locus coeruleus (Feldman, Mitchell, & Nattie, 2003; Oyamada, Ballantyne, Mückenhoff, & Scheid, 1998) as well as the fastigial nucleus in the cerebellum (Martino et al., 2007). These areas are beyond the blood brain barrier and thus, do not respond to changes in blood gas levels, but rather changes to pH in cerebrospinal fluid (via changes in H^+ concentration) (White, 2005).

Peripheral chemoreceptors are located in the carotid bodies at the joining (bifurcation) of carotid arteries, and in the aortic bodies, both above and below the aortic arch. The carotid body responds to changes in arterial pH, pO_2 and pCO_2 and the aortic chemoreceptors respond only to pH and pCO_2. The carotid chemoreceptors exert more of an influence over respiratory control than those in the aortic bodies. Peripheral chemoreceptors are the only receptors that mediate change in ventilation in response to hypoxia (Lahiri et al., 2006), and complement the central chemoreceptors in responding to changes in pCO_2 (West, 2008). Feedback from the carotid body to the respiratory centres is via glossopharyngeal nerves, and from the aortic body to respiratory centres is via the vagus nerve (Tortora & Grabowski, 2000). The peripheral chemoreceptors receive a high blood flow, which enables them to rapidly respond to changes in blood gas concentrations, albeit not as great a contribution of response to changes in pCO_2 as central chemoreceptors (Smith, Rodman, Chenuel, Henderson, & Dempsey, 2006).

3.8.3 Respiratory System Afferents

Afferent feedback from receptors in the chest wall, respiratory muscles and lungs provides input to the brainstem respiratory centres via the vagus nerve as well as thoracic and cervical nerve roots (the initial segment of the nerve leaving the central nervous system). The receptors involved in respiratory feedback mechanisms are divided into three main types: 1) stretch receptors, 2) C-fibres (including irritant and ‘J’ receptors) and 4) proprioceptors (Widdicombe, 2009). There are slowly- and rapidly-adapting stretch receptors (SARs and RARs, respectively) that are located within the airway walls. SARs are large, myelinated fibres within smooth muscles of the airways (Schelegle & Green, 2001). Changes in lung volume and transpulmonary pressure stimulates SARs which has an influence on respiratory timing. SAR sensitivity is increased during bronchoconstriction, airway obstruction or reduced lung compliance, which is thought to be as a result of smooth muscle contraction (Davenport et al., 1981).

RARs are thinner, myelinated fibres that are widely distributed within and below the epithelium of the lower respiratory tract. RARs are sensitive to mechanical stimuli such as changes to tidal volume, respiratory frequency or inspiratory/expiratory flows and chemical stimuli such as cigarette smoke, dust, pro-inflammatory chemicals or inhalable substances such as heroin or crack cocaine. They are also referred to as irritant receptors (Sant'Ambrogio & Widdicombe, 2001). Stimulation of RARs leads to cough, airway vasodilation, mucous hypersecretion, hyperpnoea (increase in depth and rate of breathing), and other cardiovascular responses (Sant'Ambrogio & Widdicombe, 2001).

J receptors are unmyelinated fibres that respond to chemical changes in the pulmonary and bronchial circulations. These receptors are triggered by chemical irritants such as capsaicin, histamine, prostaglandins and bradykinin (Widdicombe, 2001). Stimulation of these receptors causes an increase in respiratory rate, broncho- and laryngeal constriction and increased upper airway mucous secretion. There is great overlap between these receptors and RARs and in their responses to stimuli.

Proprioceptors are sensitive to changes in muscle tension and length and are present in the tendon organs and muscle spindles of the respiratory muscles. When mechanoreceptors are activated, reflex inhibition of inspiratory activity is created in response to rib elevation (De Troyer, 1997).

3.8.4 Impaired Gas Exchange

Impaired gas exchange is the most common issue in any damage to the respiratory system through lung disease or injury to the lungs (including indirectly through consumption of opiates). An impairment to gas exchange causes hypoxaemia (abnormally low pO_2 in arterial blood), and hypercapnia (increased arterial pCO_2) if there is alveolar hypoventilation. The main causes of hypoxaemia are ventilation-perfusion inequality, shunt (whereby the air cannot reach alveoli that are adequately perfused by pulmonary capillary blood, i.e. the ventilation/perfusion ratio[9] is zero) or hypoventilation. Reduced ventilation of alveoli, where gas exchange takes place, is termed alveolar hypoventilation. As described in the alveolar ventilation equation, there is an inverse relationship between alveolar ventilation and alveolar

[9] The ventilation/perfusion ratio (V/Q ratio) is used to assess the efficiency and adequacy of matching between ventilation (the air that reaches the alveoli) and perfusion (blood that reaches the alveoli via capillaries).

PCO_2. Consequently, when alveolar ventilatory rates fall, the rate at which carbon dioxide is eliminated by the lungs also decreases, thus yielding increased alveolar and arterial partial pressures of alveolar carbon dioxide (West, 2011). Hypoventilation is thus always accompanied by increased alveolar carbon dioxide values and in turn hypercapnia. As per the alveolar gas equation, an increase in the alveolar partial pressure of carbon dioxide result in a reduced alveolar partial pressure of oxygen (P_AO_2). A reduction in P_AO_2 will lead to a reduction in the arterial partial pressure of oxygen (PaO_2) (West, 2011):

$$P_ACO_2 = VCO_2/V_A \times K$$

P_ACO_2 = alveolar PCO_2,

VCO_2 = CO_2 output

K = constant

Many different conditions lead to hypoxaemia caused by hypoventilation and for many of these, the lungs are themselves normal. Opioid use leads to a blunted response to hypercapnic/hypoxaemic states (Weil, McCullough, Kline, & Sodal, 1975). Therefore, the hypercapnic ventilatory response of a chronic opioid user will be dampened and shifted to the right (Figure 3-6, line B) (Pattinson, 2008; Teichtahl et al., 2005; Weil et al., 1975). Specific description of opioid effect on respiratory control is discussed further on in this chapter.

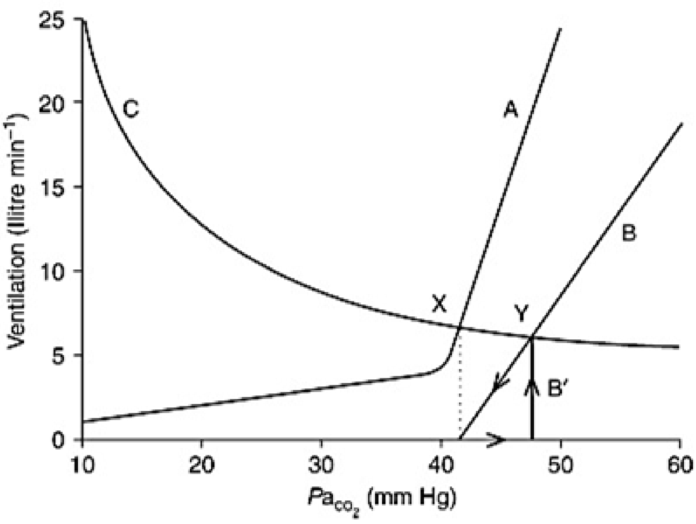

Figure 3-6: Carbon Dioxide Response Curve.
Curve A represents the normal ventilatory response to carbon dioxide in an awake individual. Line B represents a 50% depression of the HCVR caused by opioid administration. Apnoea can occur here but P_ACO_2 must rise to steady-state values (i.e. along the *x*-axis) for breathing to recommence (line B'). Curve C represents the carbon dioxide excretion hyperbola and demonstrates how changes in ventilation affect P_ACO_2. Point X represents the awake state and point Y represents opioid-depressed breathing. Despite a 50% depression of the HCVR, the carbon dioxide changes only relatively modestly (Pattinson, 2008).

The delivery of oxygen to tissues is the product of arterial oxygen content, and cardiac output. The oxygen content of arterial blood is mainly related to haemoglobin which greatly increases the oxygen-carrying capacity of the blood. When oxygen binds to deoxyhaemoglobin, the structure/conformation of the protein changes and is known as oxyhaemoglobin. When oxygen is unloaded, haemoglobin has a lower affinity (binding capacity) for oxygen (Thomas & Lumb, 2012). Hence the binding capacity changes with each additional oxygen molecule, and hence the saturation of haemoglobin is not a linear one. The well-known sigmoidal dissociation curve of oxyhaemoglobin represents the relationship between oxygen levels and haemoglobin saturation (Figure 3-7). The partial pressure of oxygen at which haemoglobin is 50% saturated is known as P_{50}. When the affinity to oxygen increases, the curve is shifted to the left, thus the P_{50} falls. Similarly, when affinity to oxygen reduces the curve is shifted to the right. The normal PaO_2 is associated with oxygen saturation of around 98-100% (Thomas & Lumb, 2012).

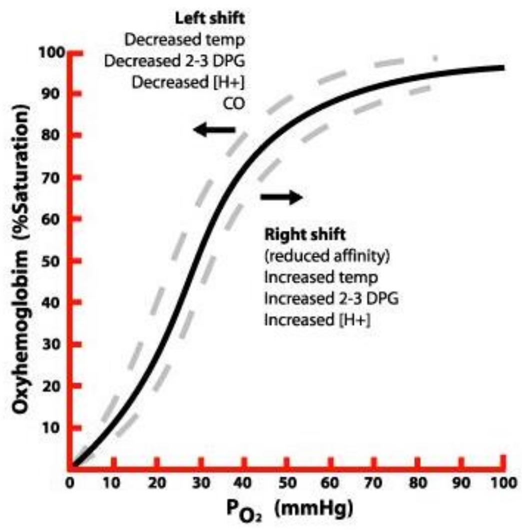

Figure 3-7: Oxygen-Haemoglobin dissociation curve (Thomas & Lumb, 2012).

The term 'respiratory failure' is used to describe a syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon dioxide elimination. There are four different types of respiratory failure but the two most relevant types for this thesis depend on whether the failure stems from hypoxaemia/failure of oxygen exchange (Type I) or hypercapnia/failure to exchange or remove carbon dioxide (Type II) (Gunning, 2003). Type III occurs during the perioperative period and Type IV results from hypoperfusion of respiratory muscles, when patients are in shock.

An increase in arterial PCO_2 causes an increase in blood carbon dioxide concentration, which will lead to a decrease in pH in the blood, i.e. a respiratory acidosis (Epstein & Singh, 2001). Hypercapnia and respiratory acidosis can occur with any disease process where there is an issue with the neural control of ventilation, mechanics of ventilation or alveolar gas exchange resulting in alveolar hypoventilation, ventilation-perfusion mismatching or both.

3.9 Opioids and Respiratory Control

The opioid sensitive aspects of respiration are within rhythm generation. At low opioid doses, changes in respiratory pattern are observed over changes in tidal volume (Lalley, 2003). At higher opioid doses, tidal volume is shown to reduce, which may be due to decreased tonic inputs from opioid sensitive chemoreceptors. Opioid-sensitive chemoreceptors are partly compensated by increases in pCO_2. There are suggested mechanisms of how opioids can cause an irregular respiratory pattern when administered (Bouillon, Bruhn, Roepcke, & Hoeft, 2003; Lumsden, 1923).

During inspiration the pre-Bötzinger complex is active and is inhibited by opioids, whereas the RTN/pFRG is active during expiration and is insensitive to opioids (Janczewski & Feldman, 2006). This difference in sensitivity to opioids shows differing mechanisms of opioid-induced respiratory depression (Mellen, Janczewski, Bocchiaro, & Feldman, 2003). When the mu-opioid receptor agonist DAMGO was applied to rat brainstem slices containing only pre-Bötzinger complex, it gradually slowed the respiratory rhythm (Mellen et al., 2003). Further to this, when DAMGO was applied to a preparation with both RTN/pFRG and the pre-Bötzinger complex, the rhythm still slowed but with a change in the pattern. The breathing pattern became irregular due to the skipped inspirations and led to increased inspiratory periods. Subthreshold action potentials were observed during these periods of skipped breaths, which was thought to be caused by an intermittent reduction of the output signal from the pre-Bötzinger complex (Janczewski & Feldman, 2006; Mellen et al., 2003). This pattern was labelled ‘quantal’.

There is evidence that the Kölliker-Fuse and parabrachial nuclei of the pons also contribute to irregular respiration (Lalley, 2005). The Kölliker-Fuse is thought to regulate the transition from inspiration to expiration. There are also novel experimental receptor modulators (e.g. serotonin receptor subtype 4a agonists, or Dopamine D1 agonists) that have been used to investigate opioid-induced respiratory depression, however, none of these have yet to be successfully translated into humans (Pattinson, 2008).

In relation to opioid effect on chemoreceptors, literature related to peripheral chemoreceptors is better understood than central chemoreceptors, potentially due to the easier access for investigation. As described previously, depression of the hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR) by morphine and other opioids is well-reported (Arita, Kogo, & Koshiya, 1987; Sarton et al., 2000; Weil et al., 1975) (Figure 3-6). With regard to central chemoreceptors, localised application of opioids in areas of the brainstem showed some depressant effects on respiration (Taveira da Silva et al., 1983), and mu-opioid receptor agonists have shown to affect chemoreception in the medullary raphe and the NTS (Poole, Deuchars, Lewis, & Deuchars, 2007; Zhang, Xu, Zhang, & Liang, 2007).

3.10 How do Opioids Cause Respiratory Depression?

Heroin, morphine and other opioids with agonist activity at the mu-opioid receptor in the respiratory centre produce depressant effects soon after binding. As described, the activity in brain areas associated with inspiration is reduced by opioids, but the areas associated with expiration are unaffected, so the breathing rhythm becomes slow and irregular (Leino et al., 1999). This causes hypercapnia (elevated carbon dioxide levels in the blood) and hypoxaemia (low levels of blood oxygen). An example of the acute effect of injected heroin on blood oxygen levels is demonstrated in Figure 3-8.

In the absence of opioids, changes in arterial blood partial pressures of oxygen, carbon dioxide, and any resultant acid/base disturbance, which occur as a consequence of impaired control of breathing is sensed by central and peripheral chemoreceptors (sensors). These chemoreceptors relay information to the respiratory centres of the brain. Hypercapnia, hypoxaemia and arterial blood acidosis result in increased respiratory centre output to the respiratory muscles, to increase pulmonary ventilation and increase the rate of gas exchange in order to counter blood gas disturbance (see feedback loop mechanism in Figure 3-2). However, in the presence of opioids, this protective regulatory mechanism is blunted (Pattinson, 2008). If the ventilatory drive (or respiratory drive) is reduced for an extended period of time, the individual will hypoventilate, leading to impaired clearance of carbon dioxide in the arterial blood (hypercapnia), leading to respiratory acidosis. Vital organs and tissues no longer receive sufficient oxygen (hypoxia), ultimately leading to risk of organ failure, coma or death. In extreme cases, the individual will stop breathing (respiratory arrest). The severity of this respiratory depressant effect varies between opioids, but there is no opioid that does not have this effect.

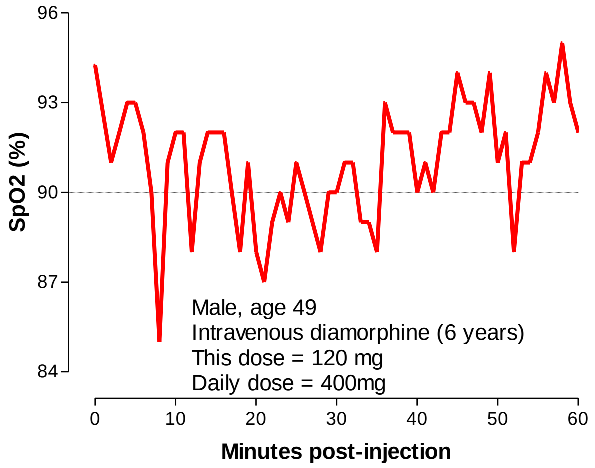

Figure 3-8: Oxygen saturation levels after intravenous opiate injection SpO_2: peripheral capillary oxygen saturation (Latt, Conigrave, Marshall, Saunders, & Nutt, 2016)

Part 3: Why is Lung Disease Relevant to Opioid Users?

This section will describe the relevance of lung disease to opioid users, the wider public health concerns and why it has become a problem that has recently received attention in the UK.

3.11 What is Obstructive Lung Disease and Why is it a Problem?

Obstructive lung disease is a category of respiratory diseases where the main feature is narrowing of the airways. Symptomatically, some of the common features of obstructive lung disease include coughing, excess mucus, persistent chest infections and breathlessness. Asthma and chronic obstructive pulmonary disease (COPD) are two of the most common chronic lung diseases in the UK. Around 1.2 million people in the UK have diagnosed COPD and around 5.4 million have asthma (BLF, 2016). Whereas asthma most commonly has an onset early in childhood, COPD (including emphysema) is most prevalent in later life (Mannino & Buist, 2007). Tobacco smoke remains the most important cause of COPD and the WHO estimates that between 40% and 73% of COPD mortality is related to smoking (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). Additionally, COPD morbidity and mortality increase with age as lung function declines in the third and fourth decades of life (Mannino & Buist, 2007). Other factors for COPD are exposure to dusts, chemicals, fumes in the workplace (Hnizdo, Sullivan, Bang, & Wagner, 2002), air pollutants (Lopez et al., 2006) and infections (Wedzicha & Seemungal, 2007).

Generally, narrowing of the bronchial tree and can occur as a result of hyperactivity or hypertrophy of the smooth muscle, airway oedema, chronic airway remodelling or mucous hypersecretion (MacNee, 2006). Obstruction in airways lower down in the bronchial tree (distal airways) can result in their collapse during expiration. This can lead to gas trapping within the lung (lung hyperinflation), as well as causing positive end-expiratory pressure (PEEP) which needs to be overcome before air can be drawn into the airway down a pressure gradient from the atmosphere (i.e. PEEP is an inspiratory threshold load). Furthermore, hyperinflation imposes an elastic load on the respiratory muscles because of the added stretch on the lung tissues as a result of increased lung volume (see section 3.7.7). These changes increase the work of breathing and typically lead to an increase in neural respiratory drive.

3.12 Opioid Users & Their Lungs

From a clinical and public health perspective, the issue of underlying pulmonary morbidity in individuals who are at risk of opioid overdose is an additional concern. In general, it is widely understood that people with mental health conditions have increased risk of physical ill-health, delayed diagnoses and higher mortality rates. Moreover, those with physical as well as mental ill-health have poorer quality of life and increased mortality (Davies et al., 2014). At a national level, this is currently an area that is recognised by the Department of Health's *No Health Without Mental Health* campaign (Health, 2012), and locally, by King's Health Partner's (KHP) Mind & Body Programme affirming the importance to 'treat the whole person' (KHP, 2017).

People seeking treatment for drug and alcohol addiction are one of the most marginalised groups who struggle to access health care in both primary care and acute secondary care settings. An additional challenge is related to the premature deaths of individuals who are in treatment for drug/alcohol addiction, for example, patients seeking treatment for heroin addiction die 15 years earlier on average than the general population (Smyth, Fan, & Hser, 2006) and drug-, and in particular, opioid-related deaths have been increasing (NRS (National Records of Scotland), 2018; ONS, 2018). A recent comprehensive inquiry into drug-related deaths highlighted that respiratory conditions contribute to these mortality figures and concluded that better pathways need to be enabled to screen for, and treat, health conditions including lung disease (PHE, 2017). Considering the high number of people who smoke and use drugs, and the increasing numbers of ageing heroin users, it is unsurprising that illnesses caused by smoking play a significant role in the causes of death and may also increase the susceptibility to opioid overdose (Jolley et al., 2016; PHE, 2016b).

Furthermore, respiratory clinicians have increasingly been noting airways disease due to the effects of opioid smoking (Jolley et al., 2016; Walker et al., 2015). A great deal of the existing literature relates to asthma and heroin inhalation (Cygan, Trunsky, & Corbridge, 2000; Hughes & Calverley, 1988; Krantz et al., 2003; Levine, Iliescu, Margellos-Anast, Estarziau, & Ansell, 2005). These studies have reported acute to severe asthma cases in heroin smokers, some requiring artificial ventilation. There are also reports that around 6% of respiratory emergency admissions occur in drug users (Canning, Kennell-Webb, Marshall, Wessely, & Peters, 1999). However, very little is actually known of the link between heroin administration and lung disease, let alone of overdose risk. A brief report on the prevalence of respiratory symptoms and lung disease in a community drug and alcohol treatment centre showed that 37% of clients (mixed sample of clients seeking treatment for drug and/or alcohol addiction) showed signs of COPD. Of the 112 clients that were tested 88% were smoking tobacco and 66% were heroin smokers (Jolley et al., 2015a). There are a further studies on COPD and heroin smoking (Burhan et al., 2018; Buster, Rook, et al., 2002; Lewis-Burke et al., 2016; Walker et al., 2015). They show that impairment of lung function (using either measures of Forced Expiratory Volume in the first second or CT scan of the lungs) is suggested to be related to smoking heroin.

However, not all heroin users smoke heroin but despite this, it appears that many have pulmonary infections or diagnosed or undiagnosed lung disease, including COPD (Hind, 1990; Jolley et al., 2016; Scheidegger & Zimmerli, 1989; Walker et al., 2015). Tobacco smoking could play a role in the development of lung disease, and this is clearly a complex and multifactorial issue. Between 84% and 98% of opioid users smoke tobacco, which is the highest prevalence among all drug users (Bowman et al., 2012; Clemmey, Brooner, Chutuape, Kidorf, & Stitzer, 1997; Guydish et al., 2011; Pajusco et al., 2012; Tacke, Wolff, Finch, & Strang, 2001). Additionally, drug users who smoke have a heightened risk of premature death than non-smokers (Hser, McCarthy, & Anglin, 1994). There is a great need to establish a stronger connection between clinical and experimental investigation of the respiratory system with opioid-induced respiratory depression and overdose risk.

3.13 Known Unknowns of Overdose Deaths

For the past 40 years, a number of different studies have attempted to understand the contributing mechanism in fatal overdose (Cherubin, McCusker, Baden, Kavaler, & Amsel, 1972; Darke & Duflou, 2016; Darke, Duflou, & Torok, 2010a; Darke, Mattick, & Degenhardt, 2003b; Davoli et al., 2007; Force, Fisher, & Millar, 1973; Byers et al., 1975; White & Irvine, 1999). Pulmonary oedema (fluid in the lungs) is considered the main factor and frequently observed in autopsy reports through histopathological evidence or congested lungs (Sporer & Dorn, 2001; White & Irvine, 1999).

Pulmonary oedema in the heroin using population is considered to be the most common and widely reported complication of overdose (Duberstein & Kaufman, 1971; Hind, 1990; Schachter & Basta, 1973; Warner-Smith et al., 2001; White & Irvine, 1999). However, these findings are not specific to opioid-related deaths, but instead to deaths caused by respiratory failure. Additionally, pulmonary oedema and aspiration of vomit may not necessarily cause a fatality but may, in subsequent overdose events, lead to an increase risk of fatality (White & Irvine, 1999). Furthermore, opioids have an emetic effect and can also create the risk of aspiration of vomit (Henry, 1999). Whilst there can be a good prognosis and recovery from pulmonary oedema, it may leave impairment. In a study of 58 overdose survivors with pulmonary oedema (Duberstein & Kaufman, 1971), some showed lower vital capacity and total lung capacity after the non-fatal overdose event. Pneumonia also appears to develop after pulmonary oedema in some cases. Bacterial pneumonia is often as a result of aspirated vomit (Duberstein & Kaufman, 1971) but detailed studies on this are lacking as follow-up is inherently difficult (Darke & Duflou, 2016; Schachter & Basta, 1973). Moreover, there is also an issue related to the asymptomatic nature of certain conditions. Even after years of smoking tobacco, heroin and/or crack, emphysema may not be symptomatic enough for a user to seek treatment, however, autopsy reports often show that there is presence of undiagnosed pneumonia (Warner-Smith et al., 2001). This could be related to the respiratory depressant effects of opioids, and is certainly a crucial question of this thesis.

Part 4: How do we Measure Respiratory Depression in Opioid Users?

This final section of the chapter will provide a justification of the measures used in this thesis. As there is no gold standard measure of respiratory depression it is important to provide good reason for inclusion of these varied measurements. This thesis incorporates a number of different parameters as it is ideally most effective to use multiple parameters at the same time to detect whichever indicator of respiratory depression may initially arise or is most effective at detecting changes (Gupta & Edwards, 2018).

3.14 Justification of Physiological Measures

3.14.1 Parasternal Intercostal Muscle Electromyography (EMG_{para}) and Neural Respiratory Drive (NRD)

Neural respiratory drive (NRD) refers to the motor output from the central nervous system to the respiratory muscles acting on the chest and abdominal wall, generating respiratory movements necessary to pump air in and out of the lungs during inspiration and expiration. NRD differs according to the proportion of loads placed on the respiratory system and any changes in capacity of the respiratory muscle to respond to these loads (Moxham & Jolley, 2009). Any increase in the load and/or reduction in capacity leads to increased NRD.

It is not currently possible to accurately measure NRD using direct measures of the total brainstem respiratory neural output. Further, while it is possible to measure NRD as phrenic nerve activity in anaesthetised animals (Adrian & Bronk, 1928), this is not feasible in awake human participants. Pressure-based measures do exist but are restricted in their accuracy (Gaultier, Perret, Boule, Buvry, & Girard, 1981; Whitelaw, Derenne, & Milic-Emili, 1975) as they are reliant on patient motivation and cooperation as well as influenced by impaired lung mechanics, as occurs in disease such as COPD which are characterised by obstruction of the airways. These measures examine the respiratory pressures as indices of respiratory muscle tension (which indicate the activation of a muscle). Fortunately, there are other potential surrogates of NRD that can be measured relatively easily. These are highlighted in figure 3-9. Respiratory muscle activity and ventilation are possible ways in which NRD can be measured. Measurement of the neural input to selected and relevant respiratory muscles is possible and overcomes any limitation that may occur by use other ways of measuring NRD. NRD is able to reliably characterise the load imposed on the respiratory system relative to its capacity.

Electromyography (EMG) is a technique that is used to measure electrical activation of skeletal muscle associated with muscle contraction (Lindstrom & Magnusson, 1977). EMG can be measured using surface electrodes placed over the muscle of interest, needle electrodes inserted into the muscle or catheter-mounted electrodes in the oesophagus. The magnitude of the EMG signal is directly related to the force generated by the muscle during a contraction.

Details of the anatomy and neurophysiology relating to parasternal intercostal muscles are described earlier in this chapter. Between the sternum and costo-chondral junction (the joint between rib and costal cartilage on the front of the rib cage), the first five interspaces are replaced by flat broad tendons (fibrous aponeuroses), and the internal intercostals in these interspaces are known as parasternal intercostal muscles (Han et al., 1993) (Figure 3-3). The parasternal intercostals have a role in inspiration and are termed the 'inspiratory intercostals'. Parasternal intercostal muscles are obligate muscles that activate in synchrony with the diaphragm and only inactive when inspired volume of air is minimal (De Troyer & Estenne, 1988; De Troyer & Sampson, 1982; Gandevia et al., 1996; Taylor, 1960). There is also a well-reported and strong agreement between EMG activity of the parasternal intercostal muscles and the diaphragm (Reilly et al., 2013, 2011; Wanke, Lahrmann, Formanek, & Zwick, 1992). EMG of the parasternal intercostal muscles (EMG_{para}) use in measuring NRD has also been shown to be reproducible (Gandevia et al., 1996; Murphy et al., 2011; Reilly et al., 2011; Steier, Jolley, Polkey, & Moxham, 2011). The parasternal muscles show less mechanical disadvantage than the diaphragm in the presence of lung hyperinflation (Decramer, Jiang, & Demedts, 1987) (an abnormally high volume of air remaining in the lungs at the end of expiration) and have greater mechanical efficiency at total lung capacity. It is suggested that parasternal intercostal muscles, in comparison with the diaphragm, may actually be preferentially recruited under conditions of increased and expiratory lung volume (Jiang, Deschepper, Demedts, & Decramer, 1989).

EMG_{para} has been used in various different clinical settings and laboratories and has successfully been used to detect changes in respiratory load and NRD in a number of different patient populations (Gandevia et al., 1996; Murphy et al., 2011; Reilly et al., 2011; Steier, Jolley, Polkey, & Moxham, 2011), including opioid users (Jolley et al., 2015b). Two studies (Murphy et al., 2011; Reilly et al., 2011) examined the reproducibility of EMG_{para} in healthy young adults and showed strong correlation of values obtained across two occasions. Measuring EMG_{para} is a useful tool in discriminating between healthy subjects and those with respiratory disease. Greater levels of EMG_{para} (i.e. increased electrical activity of the inspiratory muscles) are observed in patients with COPD (Gandevia et al., 1996; Murphy et al., 2011), asthma (Steier et al., 2011) and cystic fibrosis (Reilly et al., 2011) compared to healthy subjects.

EMG_{para} is thus widely accepted to be an indirect index of NRD, thereby providing an objective quantifiable index of the load on the respiratory muscles and the load-capacity balance of the respiratory muscle pump. The existing literature is in support of the use of EMG_{para} as a marker of NRD and load on the respiratory system. These observations support the use of EMG_{para} as a direct, reliable and sensitive measure of acute opioid-induced changes in NRD, as described in this thesis.

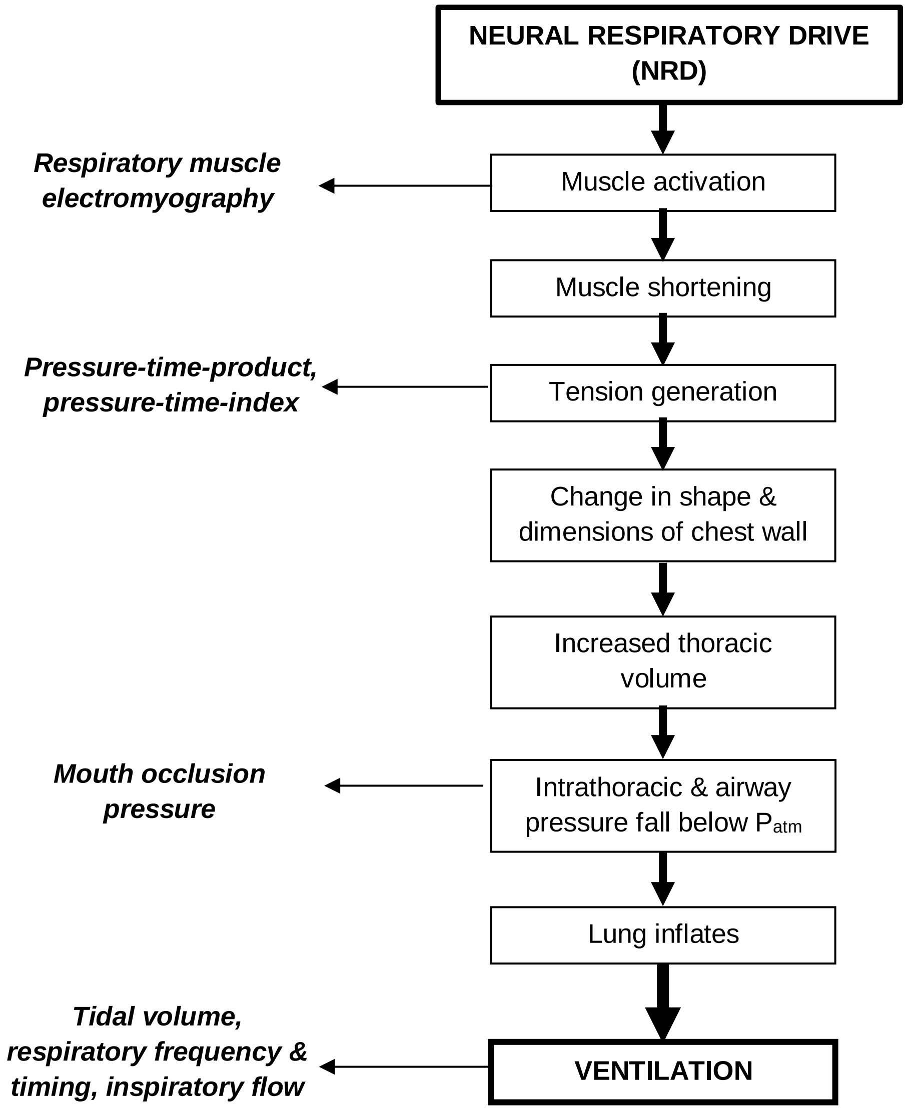

Figure 3-9: A flow diagram outlining the physiological coupling of NRD to ventilation, indicating the opportunities for clinical measurement of NRD (Jensen, Pattinson, & Jolley, 2016). P_{atm} = atmospheric pressure

This figure highlights the links between NRD, respiratory muscle activation, chest wall and lung mechanics as well as ventilation. It can also be seen here that the potential for ‘uncoupling’ of mechanical output from NRD is increased with each move away from the central respiratory centre. The implication of this when measuring NRD in patients with respiratory disease, which applies to opioid users, is that the measures further away from respiratory centres such as ventilatory parameters become more unreliable measures of NRD in respiratory disease as the mechanical outputs are uncoupled from NRD.

3.14.2 Ventilation

Although often used as a measure of NRD, ventilation is not a perfect measure of NRD because changes in the mechanical properties of the respiratory system will alter the relationship between NRD and inspiratory flow. This is crucial to the study of NRD in COPD where indices of NRD based on ventilation will unreliably underestimate the level of NRD (Cherniack & Snidal, 1956). Changes in the mechanical properties of the respiratory system alter the relationship between NRD and ventilation. This is important when studying NRD in people who have COPD, where indices of NRD based on ventilation are unreliable as they will underestimate the level of NRD (Cherniack & Snidal, 1956).

Most studies that examine the neural control of respiration use ventilation as an outcome measure. Ventilation parameters are centred on measuring the volume and frequency of inspired and expired air as well as combinations of these. Usually these are conducted via a face mask or mouthpiece attached to a pneumotachograph[10], which essentially allows an accurate and reliable type of flow measurement. Minute ventilation (V_E) is the product of the tidal volume (VT) and respiratory frequency (breathing rate; Vf). As these can both be regulated separately, a more complete assessment of the impact of respiratory stimuli (anything that causes a change in the respiratory response mechanisms such as a decrease in oxygen or increase in stress) on NRD also requires assessment of both tidal volume and respiratory frequency) (Cherniack & Snidal, 1956; Milic-Emili & Grunstein, 1976).

[10] Pneumotachographs work by ensuring constant resistance to measure pressure changes as the flow varies.

3.14.3 End-tidal CO_2 ($ETCO_2$) and Transcutaneous CO_2

Capnography is a measure of carbon dioxide in respiratory gases and can be used to reliably measure different carbon dioxide outputs in a non-invasive manner. End-tidal CO_2 ($ETCO_2$) and transcutaneous CO_2 ($TcCO_2$) are two capnography measures incorporated in this thesis. The most reliable, and 'gold standard' measure of blood gases such as carbon dioxide and oxygen is via arterial blood gas tests (ABG) or by earlobe blood gas test (EBG), which is an arterialised capillary sample. However, its application has some limitations; arterial blood gas tests are invasive, time consuming, expensive and can be unpleasant and risky (Parker & Gibson, 2007; Yousuf et al., 2015).

In addition, single measurements of partial pressure of carbon dioxide are unhelpful in predicting impending respiratory depression (Gross, 2003). Modelling of this interaction between carbon dioxide and opioids on breathing has shown that with gradual increase in opioid levels, progressive respiratory depression causes gradual hypercapnia. However, with a fast intravenous bolus injection of opioid, respiratory depression is reached until pCO_2 reaches its steady-state (Pattinson, 2008). This goes some way in explaining why drugs with slower binding to receptors (low affinity), e.g. morphine, are considered safer than those that bind more quickly e.g. fentanyl. This modelling also demonstrates the inability of single point carbon dioxide measuring to reliably detect respiratory depression.

End-tidal carbon dioxide ($ETCO_2$) measurements refer to the peak carbon dioxide concentration or partial pressure of carbon dioxide recorded at end-expiration. $ETCO_2$ measurements uses infrared light passing over the gas sample within each exhaled breath. The presence or lack of carbon dioxide is inversely related to the amount of light that passes through the sensor (low levels are indicated by high amounts of light, and vice versa) (Bickler, 2007). $TcCO_2$ is another measure of carbon dioxide that uses continuous, instead of per breath measurements. Both have been shown to reliably detect hypercapnia but are not considered to be as accurate as $PaCO_2$ (Won et al., 2016; Yousuf et al., 2015).

Capnography can relay information on metabolism, perfusion and ventilation or even how effectively carbon dioxide is produced, transported and eliminated by the alveoli, in an immediate setting. An advantage of the $ETCO_2$ method is that changes are detected and displayed breath-by-breath, allowing acute changes in alveolar (and hence arterial) CO_2 levels to be measured. $TcCO_2$ is more commonly used in polysomnography (sleep studies) where trends are reported over extended periods of time. Carbon dioxide is highly soluble in tissue and readily diffuses through the skin. $TcCO_2$ uses sensitive sensors over the skin and is a well-validated surrogate marker for $PaCO_2$ and is considered more reliable, in this sense, than $ETCO_2$ (Gerdung, Adeleye, & Kirk, 2016). Additionally, in awake individuals the discrepancy between $TcCO_2$ and $ETCO_2$ is not as significant as during sleep (N. L. Jones, Robertson, & Kane, 1979; Won et al., 2016).

3.14.4 Pulse Oximetry

Measurement of arterial blood oxygen saturation and its physiological foundations are described in this chapter. Non-invasive assessments of arterial blood oxygen saturation (SpO_2) by pulse oximetry is a simple and common monitoring tool used in almost every clinical setting. Strict guidelines exist within anaesthesiology and emergency medicine in the use of SpO_2 to monitor for respiratory function during sedation, deep sedation or general anaesthesia, amongst other states. The detection of arterial hypoxaemia is crucial in these clinical areas (Becker & Casabianca, 2009). Hypoxaemia is distinct from hypoxia in that it occurs when ventilation is adequate but perfusion of the pulmonary alveoli is inadequate and there is a failure of oxygenation. Hypoxia is a more generic term encompassing reduced oxygen in inspired gas or any tissue, including blood. Pulse oximetry allows for a continuous, non-invasive method, again, as opposed to direct measurement of blood gases which require a sample of blood. However, a fall in SpO_2 is a relatively late feature of hypoventilation, and reliance on SpO_2 will therefore lead to under-recognition of respiratory depression in standard clinical settings (Dahan, Aarts, & Smith, 2010; Jolley et al., 2015b).

It is also important to note that pulse oximetry and capnography are only ever an indirect, approximate measure of pO_2 or pCO_2.

3.15 Current Experimental Studies on Respiratory Depression and Overdose

A great proportion of our current understanding of overdose mechanisms is as a result of controlled trials of prescribed, injectable opioids, mainly heroin. These trials have incorporated physiological measurements as part of their safety protocols (Haasen et al., 2007; March, Oviedo-Joekes, Perea-Milla, & Carrasco, 2006; Perneger, Giner, del Rio, & Mino, 1998; Reimer et al., 2011; Strang, Metrebian, et al., 2010).

There is a need to advance this type of experimental work further and develop better techniques and responses to overdose. The standard clinical practice of measuring hypoventilation involves monitoring pulse oximetry. As stated previously. it has been speculated that this approach may underestimate the true respiratory effects of the drugs (Jolley et al., 2015b). There are more sensitive approaches as well as novel, less invasive and reliable techniques that could be used to detect early indicators of respiratory depression. Transcutaneous or end-tidal carbon dioxide monitoring or direct measures of NRD via respiratory muscle EMG are more advanced, and potentially clinically useful techniques.

My second supervisor, Dr Caroline Jolley, along with colleagues in the Addictions and Respiratory Medicine fields sought to investigate whether these other, more advanced techniques, could add value in detecting changes to the respiratory effects over oximetry alone (Jolley et al., 2015b). Participants (n=10) were monitored over a course of 150 minutes post-administration of their usual diamorphine dose. EMG_{para} (a tool which assesses how hard the breathing muscles are working), pulse oximetry (measuring the blood's oxygen levels), and measurement of carbon dioxide levels in exhaled breath were all measured. It was found that there was an increase in the level of carbon dioxide per breath in eight of the ten participants and a low blood oxygen level in only four out of the ten patients. Whilst there were varying degrees of respiratory depression found in all patients, pulse oximetry failed to detect some of these events. The study also found that simply talking to a patient raised awareness and resulted in resumed breathing – and thereby masked episodes where patient was breathing unusually slowly (Jolley et al., 2015b).

The findings of this work demonstrate that acute opioid-induced respiratory depression can be detected using advanced continuous respiratory monitoring techniques, but the question is: can the use of these advanced respiratory monitoring techniques reduce the risk of opioid-related respiratory depression?

Summary

Heroin is synthesised from morphine, the main active component of opium. Opioids are a particularly interesting group of drugs that have been used for centuries (in particular opium before morphine was originally isolated) for their pain-relieving, sedative, anti-anxiety and cough suppressant effects. However, they also possess a negative side effect that has been the crux of pharmaceutical development over many decades: respiratory depression, a dangerous reduction in breathing. Opioids act on a wide range of areas of the brain and body through molecules that elicit or inhibit effects (known as receptors).

In healthy individuals, the intricately balanced network of respiratory muscles and control centres of respiration allow for adequate blood gas homeostasis. The extent of respiratory muscle activity is dependent on the load which is placed upon them, and simultaneously on their own capacity. Additionally, in the presence of opioids, this protective regulatory mechanism is stunted (Dahan et al., 2010; Pattinson, 2008). The effect on ventilatory frequency by opioids is well-reported in the literature (Bailey et al., 2000; Bouillon et al., 2003; Brunton et al., 2008; Ferguson & Drummond, 2006; Lumsden, 1923). Although mechanisms, or prevalence of assumed/documented mechanisms, of fatal overdoses are not fully understood (Sporer & Dorn, 2001), it is known that if the ventilatory drive is reduced for an extended period of time, the individual will eventually stop breathing causing respiratory failure. Furthermore, either through excessive build-up of carbon dioxide in the blood (hypercapnia), leading to respiratory acidosis or vital organs and tissues no longer receiving sufficient oxygen (hypoxia) or pulmonary oedema (fluid in the lungs), ultimately it leads to risk of organ failure, coma or death if hypoxaemia is profound. The severity of this respiratory depressant effect varies between opioids, but there is no opioid agonist that does not have this effect.

There are numerous risk factors influencing the likelihood of an overdose, including, but not limited to, the type of opioid, strength and amount of the drug that is absorbed into the blood. Individual factors, such as tolerance, current health status, duration of use and genetic influences, amongst others, add to the intricacy and complexity surrounding opioid overdose.

Opiate users usually smoke tobacco and are at risk of lung disease. In obstructive lung disease the pathophysiological changes to the muscles, tissues and airways disrupt this lung-capacity relationship such that neural respiratory drive has to increase to adapt to this change in order to maintain homeostasis.

It is possible to detect respiratory depression in individuals using reliable and accurate physiological measures. EMG_{para} is a feasible measure of NRD and is responsive to changes in respiratory load-capacity balance. Additionally, capnography is a reliable and non-invasive alternative to using classic invasive methods.

This chapter has provided a detailed overview of the mechanisms, risk factors and physiological bases of opioid overdose and has explained the use of specific markers and measures of respiratory depression. The subsequent chapter leads on to discussing the methods that were incorporated into each of the studies presented in this thesis.

4 General Methods

4.1 Preface

The clinical studies described in this thesis use physiological measures to examine respiratory depression and respiratory function amongst opioid users. Methods described in this chapter are traditionally-used clinical techniques as well as novel physiological techniques that are used as indices of neural respiratory drive (NRD), which is the motor output (signals from the brain and brainstem) to respiratory muscles. Methods involved in the subjective measures of drug effect are also stated in this chapter. A justification as to the use of these particular measures is described in the preceding chapter.

I had the opportunity to be trained in the use of all of these methods with supervision from relevantly trained professionals. I also had the opportunity to attend regular research meetings with physiologists and critical care and respiratory clinicians which allowed me to resolve methodological issues as well as present and discuss data.

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4.2 Ethical Considerations

All studies within the thesis were granted ethical approval by either the King's College Hospital Research Ethics Committee (ref: 05/Q0703/82) or London South East Research Ethics Committee (ref: 16/LO/1765). All participants gave written, informed consent.

4.3 Subjects

Study 1, Respiratory Depression & Underlying Respiratory Disease in Opioid Users (described in Chapter 5): studies were performed in healthy participants, participant with opioid addiction and non-drug-dependent participant with obstructive lung conditions. All healthy subjects were free of respiratory or neuromuscular disease. All subjects gave their written, informed consent to participate and studies were performed within the Chest Unit of King's College Hospital (KCH). Screening was conducted by Dr Caroline Jolley and anthropometric measures of height and weight as well as spirometry measures were taken by Chest Unit physiology technicians.

Study 2, Acute Opioid Overdose Study (described in Chapter 8): study participants were opioid-dependent and receiving prescribed injectable diamorphine (pharmaceutical heroin) treatment. All participants gave their written, informed consent to participate and studies were performed within the NIHR/Wellcome Trust King's Clinical Research Facility (CRF) at KCH. Screening was conducted by Addictions doctors and nurses and anthropometric measures of height and weight as well as spirometry measures were taken by clinical research nurses within the CRF at KCH.

4.4 Pre-Protocol Procedures

4.4.1 Respiratory Function Methods

ARTP-trained[11] respiratory physiology technicians within the KCH Chest Unit or clinical research nurses within the CRF at KCH conducted the pulmonary function tests in accordance with the American Thoracic Society and European Respiratory Society (ATS/ERS) standards (Miller et al., 2005). The technique was explained to each participant prior to commencement of testing. All participants were seated upright with head and neck in a neutral or slightly extended position, with a nose-clip and asked to seal their lips tightly around a mouthpiece. The participants were asked to breathe in rapidly and fully to full lung capacity, and then subsequently to perform a maximal forceful exhalation, until no more air could be expelled. Verbal encouragement was provided throughout each manoeuvre and repeated efforts were performed in order to obtain three acceptable maximal manoeuvres. Acceptable repeatability was considered when the difference between the largest and subsequent largest was no more than 5% (Miller et al., 2005).

The FEV_1 and FVC values are expressed in litres of volume of air as well as a percentage of the predicted normal for a person of the same sex, age and height. Percentage predicted values are based on a set of reference values that are collated by the Global Lung Function Initiative (Quanjer et al., 2012). A ratio of FEV_1/FVC is used to determine what proportion of a person's vital capacity they are able to expire in the first second of forced expiration.

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[11] Association for Respiratory Technology and Physiology

4.5 Physiological Measurements

There are obvious ethical implications in measuring respiratory depression and monitoring overdose in humans. Thus, a method of safely detecting respiratory depression in an acute setting appears a suitable approach in addressing this issue. A number of different traditional and novel measures can be used to detect acute respiratory depression. Rationale for the use of the particular measures relevant to this thesis are highlighted in the previous chapter (Chapter 3). This section describes the methods and procedures incorporated in this thesis.

4.5.1 Electromyography of the Parasternal Intercostal Muscles (EMG_{para})

In the two primary clinical studies, parasternal electromyography (EMG_{para}) was conducted by me with supervision from Dr Caroline Jolley. Subjects' skin was rubbed with an abrasive gel (NuPrep, Waver and Company, Aurora, Colorado, USA) and then followed by alcohol wipes prior to applying self-adhesive silver-silver-chloride electrodes (Kendall Arbo, Tyco Healthcare, Neustadt/Donau, Germany). Two electrodes to the second intercostal space (bilateral) were applied, 3cm from the midline (Figure 4-1), in accordance with existing literature (Maarsingh, Eykern, Sprikkelman, Hoekstra, & Aalderen, 2012; Murphy et al., 2011; Reilly et al., 2011). A reference electrode was placed on the acromion process of the scapula.

Study 1 (Respiratory Depression in Opioid Users): EMG_{para} was recorded during resting breathing as participants were seated in a chair with their back supported, arms resting on the armrests and feet on the footrests. Participants were asked to remain still and quiet throughout the recording period. Recording of EMG_{para} was for a minimum of 30 minutes for each participant. Some participants necessitated longer recording periods due to movement, laughter or speech. Recording was taken with a minimum 15 minutes rest after spirometry testing to reduce any alteration of NRD due to forced expiratory manoeuvres.

Study 2: EMG_{para} was recorded continuously over a 60-minute post-intervention period, plus a 3-minute baseline recording period. Participants were measured whilst seated in a semi-reclining chair that facilitated vital signs monitoring.

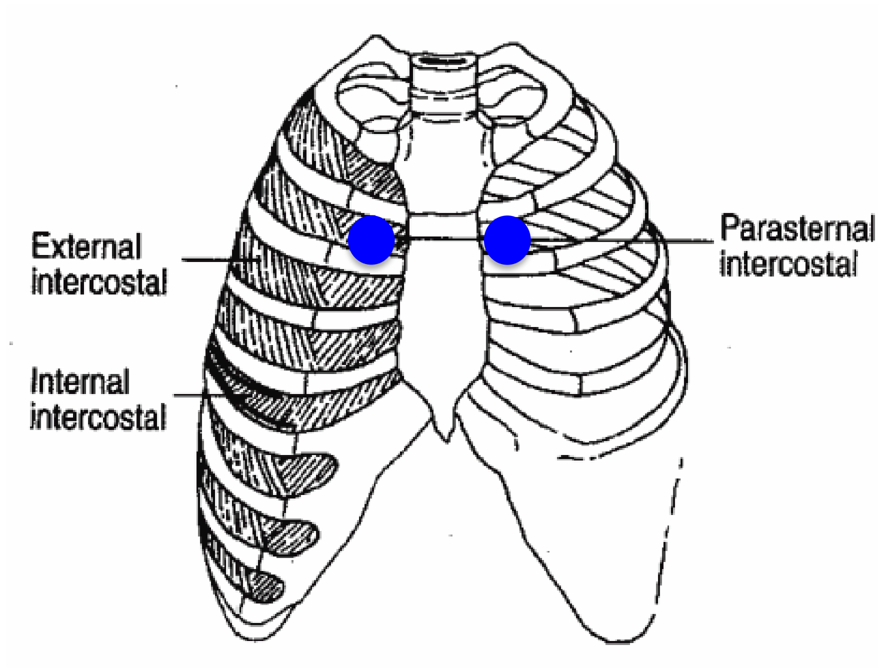

Figure 4-1: Illustration of the positioning of electrodes (blue) on the 2nd intercostal space parasternal intercostal muscles of the ribcage. (Han et al., 1993)

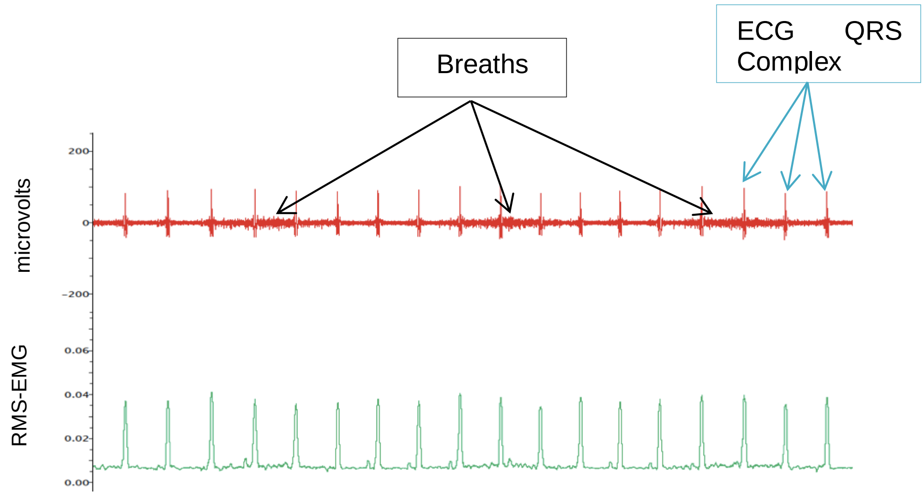

Figure 4-2a: Sample showing raw EMG_{para} (red) and root mean square (RMS) (green) traces showing three resting breaths with ECG QRS complexes also highlighted.

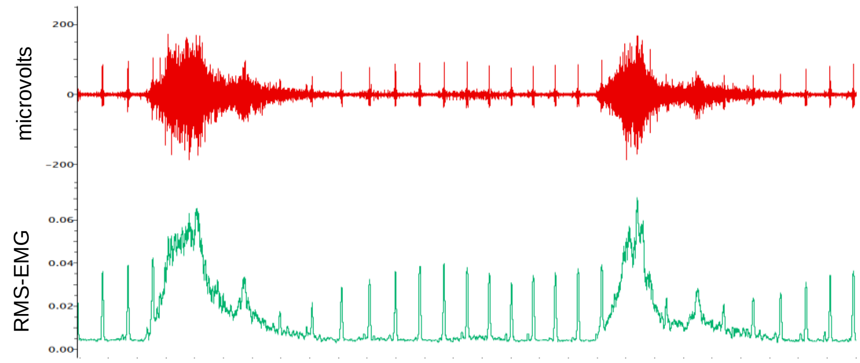

Figure 4-2b : sample of two maximal manoeuvres with raw EMG_{para} (red) and root mean square (RMS) (green).

4.5.2 EMG_{para} Acquisition

EMG_{para} signals were amplified (gain x1,000) and band-pass filtered between 10Hz and 2,000Hz (using CED 1902, Cambridge Electronic Design Ltd, Cambridge, UK). EMG_{para} signals were acquired and digitised using a Powerlab analog-to-digital converter (Powerlab, ADInstruments, Sydney, Australia) and displayed on a laptop computer (Dell Inspiron 3000) running LabChart software (Version 8, ADInstruments Pty Ltd, Castle Hill, Australia). A sampling frequency of 4kHz was used during resting breathing and maximal inspiratory manoeuvres. Following post-acquisition band-pass filtering between 20Hz and 1kHz using LabChart software, the recordings were stored for off-line analysis (MacBook Air, Mac OS X Yosemite, Apple Inc., Cupertino, California, USA). A notch filter at 50Hz to minimise mains frequency interference ('noise') was implemented. It was accepted that there would be loss of EMG_{para} signals within the 50Hz region of the EMG_{para} frequency spectrum.

4.5.3 EMG_{para} Interpretation

Areas of increased EMG activity that were characteristic of inspiration were identified (Figure 4-2a and Figure 4-2b). RMS was converted from the raw signal using LabChart. The maximum RMS value of EMG_{para} during 100ms subdivisions of each breath was determined by manually selecting signals falling between QRS complexes of the ECG artefact (Figure 4-2a). Subsequently, the mean maximum RMS EMG_{para} per breath over 1-minute subdivisions of the whole recording was calculated. EMG_{para} was expressed in microvolts (µV) and also, as a percentage of the peak RMS EMG_{para} value obtained during maximal respiratory manoeuvres such as inspiration to TLC (slow breath in all the way to maximum breath hold) (EMG_{para}%max) (Figure 4-2b). EMG_{para} from each minute of each recording was analysed. Periods of increased EMG_{para} activity characteristic of inspiration selected, manually selecting regions between ECG complexes (QRS) for analysis.

Accurately measuring and representing EMG signals depends on a number of different factors; namely, quality of contact between the electrode and overlying tissue (muscle interaction factors), which includes electrode position in alignment with the area of the muscle that is electrically active as well as muscle fibre direction; properties of the electrodes as well as amplifier design, and conversion and storage of the EMG signal from analogue to digital form (i.e. A/D conversion). These factors influence the amplitude, time and frequency domain properties of EMG recordings. EMG signals are also affected and can be contaminated by ambient noise, transducer noise and biological noise.

4.5.4 Sources of Noise

Ambient noise is generated by electromagnetic devices such as computers and power lines, amongst others. Transducer noise is generated at the connecting point between the electrode and overlying muscle tissue. Electrodes convert the ionic currents that are generated in the muscle cell membrane into an electric current that can be stored as a voltage potential and be manipulated. There are two specific types of noise that are present in the transduction of the signal: Direct Current (D/C) Voltage Potential and Alternating Current (A/C) Voltage Potential. The D/C Voltage Potential is caused by differences in the impedance between the electrode and recording surface and by redox reactions occurring in the contact region between the electrode and conductive gel ('contact gel'). The A/C Voltage Potential is generated by fluctuations in impedance between the conductive transducer and overlying tissue. Arranging the electrodes in a bipolar format suppresses the noise signals that are generated at the electrode-surface interface. In practice, the absolute electrode-surface impedance is not a critical factor because modern, high quality amplifiers have a high input impedance to reduce the differential pickup caused by mismatches in resistance as well as loss of voltage.

4.5.5 Calculation of EMG_{para}%index

All analysis was carried out offline using LabChart (version 8). The largest RMS EMG_{para} value was calculated by analysis of the block of EMG_{para} recordings. For each recording of interest, the mean maximum EMG_{para} per breath was calculated, and expressed as a percentage of EMG peak to obtain the mean EMG_{para}%max value. The 'EMG_{para}%index' or 'NRDI' was calculated by multiplying EMG_{para}%max with the respiratory rate (V_f) (Murphy et al., 2011). In summary, the RMS values for average EMG_{para} as well as the RMS value for a maximal manoeuvre are calculated as a percentage providing the EMG_{para}%max, which is then multiplied by the respiratory rate to provide the EMG_{para}%index or NRDI.

4.5.6 Ventilation

For study 1 (Lung Health study), flow measurements were calibrated prior to each study session/subject using a two-point calibration technique where two known flow rates were applied to the fine bore catheter pneumotachograph head. Zero flow was generated on one point, and on the second, a known flow rate was applied as measured by a rotatometer (KDG Mobrey, England, range 0-200l/min). The pneumotachograph was then connected to a pressure transducer (Validyne, Northridge, USA, range ±2.5cmH_2O) and a test of linearity was conducted using stepwise increases in applied flow rates as shown in figure 4-3. Participants were asked to tightly seal their lips around the mouthpiece of the pneumotachograph and resting breathing was recorded over a minimum of 10 minutes with a break after 5 minutes. A noseclip was in place throughout the measurement.

For study 2 (AOO study), a spirometer (AD Instruments) and calibration syringe (1L, AD Instruments) were used. Calibration involved connecting the pneumotachograph onto the syringe and subsequently, the flow head signal was set to zero. Once ensuring that there was no airflow through the pneumotachograph, the syringe was withdrawn at a steady rate to the full 3L, whilst ensuring that there was a negative deflection of flow on the trace. The acquired flow calibration signal was then calibrated through the Spirometer Flow function on the LabChart data acquisition software.

Offline analysis allows calculation of Tidal volume (VT), measured in litres. The flow signal provides the volume of air that is inhaled and exhaled (Figure 4-4). The volume is obtained by integrating the flow signal on a breath-by-breath basis. Minute ventilation (V_E) is a product of tidal volume and respiratory rate.

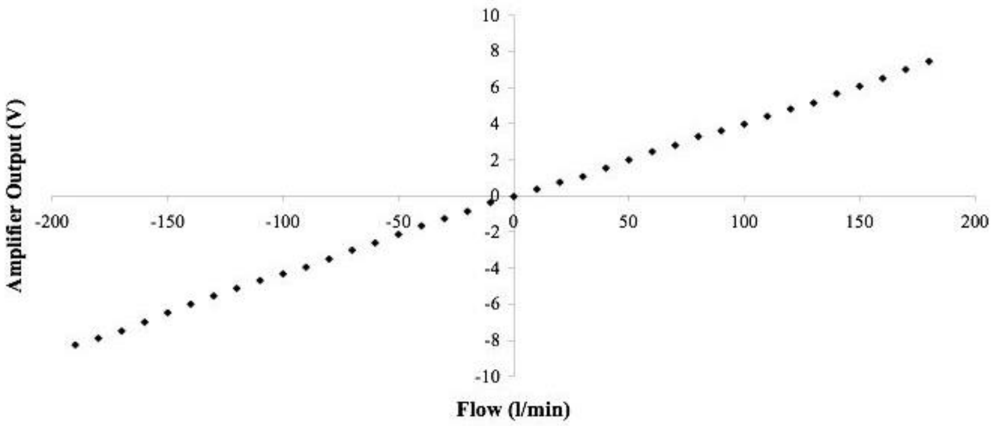

Figure 4-3: Linearity plot of the pneumotachograph-pressure transducer system to measure airflow.

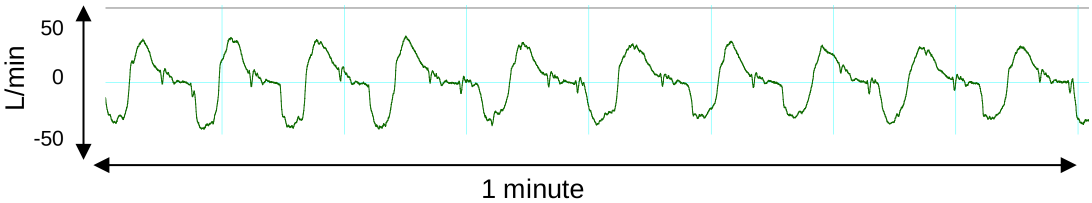

Figure 4-4: A sample of respiratory flow from a patient at rest showing 10 breaths. Negative flow is inspiratory.

4.5.7 End-tidal carbon dioxide and Transcutaneous carbon dioxide

Capnography was measured by end-tidal and transcutaneous measures. A Gas Analyser (Iworx capnograph) and a tube that attached to the nose. For measurement of end-tidal CO_2, expired air was sampled continuously from the nasal orifices using an adapted nasal cannula in line with an Iworx (Figure 4-5). End-tidal carbon dioxide ($ETCO_2$) was recorded as the peak % carbon dioxide per expired breath and converted to kPa (Figure 4-6). $ETCO_2$ was recorded continuously and displayed in real time using Powerlab and LabChart (Figure 4-6) and was stored for offline analysis.

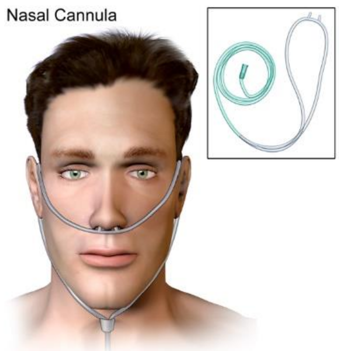

Figure 4-5: Illustration of Nasal Cannula (BruceBlaus, 2017)

Transcutaneous carbon dioxide ($TcCO_2$) was measured using a transcutaneous capnograph (TOSCA TCM4, Radiometer Medical ApS, Brønshøj, Denmark) using an ear-clip sensor. $TcCO_2$ uses sensitive sensors over the skin and is a well-validated surrogate marker for $PaCO_2$ (Gerdung et al., 2016). $TcCO_2$ uses continuous, instead of per breath measurements (Figure 4-7).

The Radiometer TOSCA device uses earlobe sensors for $TcCO_2$ measurement as well as a reflection sensor for pulse oximetry. The sensor is heated to 42ºC in order to increase capillary arterialisation and improve measurements conditions once placed on the skin. The TOSCA consists of an automatically calibrated modus before it is attached to the earlobe, using a dry gas mixture. The sensor was placed according to instructions and data was collated after an optimisation period of 10 minutes.

Data were analysed offline using a laptop as above. All capnography data were analysed in kilopascals (kPa). $TcCO_2$ data was acquired as millimetres of mercury (mmHg) and $ETCO_2$ as a percentage, and thus, all values were converted to kPa (%:kPa = 1:1.01).

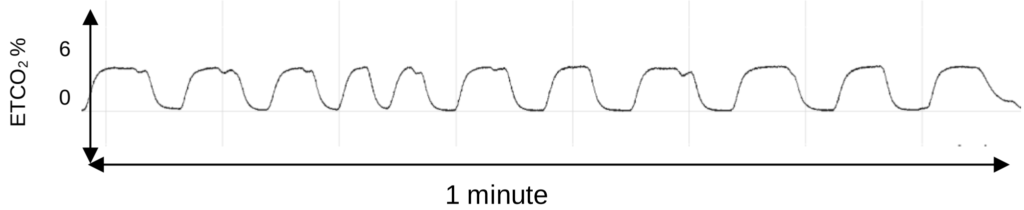

Figure 4-6: A sample of $ETCO_2$ across 1 minute.

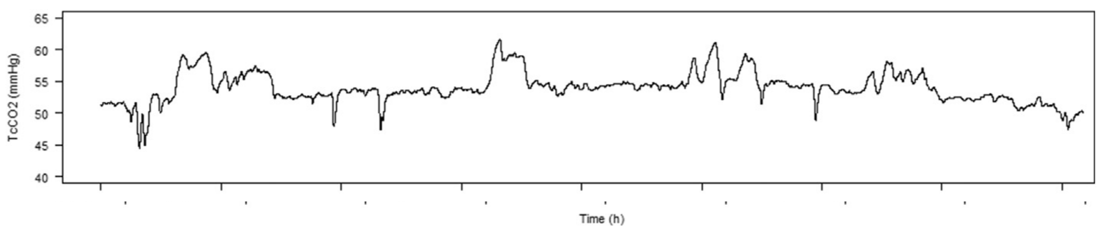

Figure 4-7: An example sample of $TcCO_2$ (Orlikowski et al., 2016).

4.5.8 Pulse Oximetry

Oxygen saturation (SpO_2) is a simple and common monitoring tool used in almost every clinical setting. Strict guidelines exist within anaesthesiology and emergency medicine for the use of SpO_2 to monitor for respiratory function. SpO_2 was recorded by pulse oximetry (Ohmeda Biox 3700) and by earlobe sensor (TOSCA). The input to LabChart was calibrated with respect to the analogue output of the oximeter before each study session. The pulse oximeter was displayed and recorded continuously on LabChart in real time and stored for offline analysis. The measures of oxygen saturation were recorded continuously with the oximeters recording a percentage of blood oxygen saturation (SpO_2%) every 5 seconds. Recording started after attachment of the finger probe on the participant.

4.5.9 Assessment of Shortness of Breath

Shortness of breath, or dyspnoea, is a subjective experience. However, quantitative measures of dyspnoea are valuable. The standardised modified Medical Research Council (mMRC) Dyspnoea Scale (Hajiro et al., 1998; Mahler & Wells, 1988) uses a scale of 0 to 4 to measure a person's functional limitation associated with breathlessness (Table 4-1). This scale was used in study 1 (Chapter 5) of the thesis.

Table 4-1: mMRC Dyspnoea Scale used to describe breathlessness in Study 1 .

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house, or I am breathless when dressing.

4.6 Indicators of Significant Respiratory Depression

Several different studies were examined when determining the most appropriate cut-off as a representation of respiratory depression. Any presence of the markers and frequencies of dips or increases below/above certain levels were realised to be the most accurate representation of the data. Evidence of significant respiratory depression was recorded using a variety of physiological markers. Criteria and threshold levels are indicative of clinically-significant respiratory depression and were determined through Sleep Medicine and Anaesthesia literature (Dahan et al., 2010; Douglas, 2005; O'Driscoll, Howard, & Davison, 2008) and through discussions and advice from members of the respiratory medicine research group which included critical care consultants, respiratory medicine consultants, and other allied experts as well as academic supervisors and co-investigators.

In study 1 (Chapter 5), an observational study where no intervention was implemented, respiratory depression was deemed to have occurred if any one of the following criteria were satisfied:

- $ETCO_2$ > 6.6kPa in one or more breaths,
- Mean $TcCO_2$ > 6kPa,
- SpO_2% <90% for longer than 10 seconds;
- Absence of inspiratory airflow and/or parasternal intercostal muscle EMG activity for more than 10 seconds (apnoea).

In the heroin study (Chapter 8), where the intervention was injectable diamorphine, the following indices of significant respiratory depression were recorded and used as evidence for respiratory depression:

- Presence of oxygen saturation <90% for longer than 10 seconds or <80% for more than 1 minute,
- $ETCO_2$% per breath exceeding 6.6kPa or increases of 1kPa from baseline,
- Mean above 6kPa $TcCO_2$ or increases of 1kPa from baseline,
- Absence of inspiratory airflow and/or parasternal intercostal muscle EMG activity for more than 10s (apnoea),

- Absence of response to verbal stimuli.

As a comparison, the following values and ranges are considered to be ‘normal’ in healthy adults with healthy respiratory function during resting breathing:

- SpO_2 above 95%;
- Mean $TcCO_2$ between 5-6kPa;
- Mean $ETCO_2$ between 5-6kPa, and no breaths exceeding 6.6kPa.

4.7 Subjective and Staff Rating of Drug Effect

Subjective drug effect measures were calculated in the studies described in chapters 6 and 8. The following variables were measured:

- Staff rating of intoxication,
- Staff level of consciousness,
- Subjective drug effect (Chapter 8 only),
- Subjective drug liking (Chapter 8 only),
- Level of intoxication,
- Pupil size, in mm.

In Chapter 6 and 8, at 3 minutes prior to administration of the injectable opioid, and then at 3, 8, 15, 30, 60 minutes each participant was asked to rate their subjective drug experience. At these times, pupil sizes were also recorded, and staff ratings of level of consciousness and intoxication were also documented against the Glasgow Coma Scale (GCS (Teasdale & Jennett, 1974)) (Table 4-2).

In Chapter 6, the following ratings were used:

Staff rating of intoxication was measured on a scale which follows the rating: 0 = no effect; 5 = maximal effect. Staff rating of level of consciousness was assessed using a numerical rating scale, as follows: 1 = normal, 2 = visibly affected but alert, 3 = drowsy but responds to verbal stimuli, 4 = no response to verbal stimuli. Patients assessed their drug-related 'high' on a rating scale, which follows the rating as follows: Rating of intoxication 0 = no effect, 5 = maximal effect

In Chapter 8, a 100mm visual analogue scale was used for all measures of subjective drug experience.

Table 4-2: Glasgow Coma Scale (Teasdale & Jennett, 1974).

Behaviour	Response	Score
Eye opening Response	Spontaneously	4
	To speech	3
	To pain	2
	No response	1
Best verbal response	Orientated to time, place and person	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Best motor response	Obeys commands	6
	Moves to localised pain	5
	Flexion withdrawal from pain	4
	Abnormal flexion	3
	Abnormal extension	2
	No response	1
Total Score	Best response	15
	Comatose Client	8 or less
	Totally Unresponsive	3

4.8 Statistics

Where appropriate, data were tested for normality and any ordinal data were presented as median (interquartile range) and non-parametric testing was used. In respiratory health study (Chapter 5), Kruskall-Wallis or Spearman Rank was used to assess the relationship between matched pairs of data and also, Mann Whitney U for differences between groups. Data analyses were performed using SPSS software v22 for Mac (SPSS Inc, Chicago, Illinois, USA). Significance was determined at values of $p<0.05$ level.

In the heroin study (Chapter 8), differences between baseline, minimum and successive time-points after drug administration were analysed using non-parametric repeated measures ANOVA (Friedman test). Friedman's test, Kruskal-Wallis was used to test for differences between baseline, minimum/maximum or successive time-points for each measure after drug administration. In addition, post hoc analysis was conducted using Dunn's Multiple Comparison Test. Differences between diamorphine dose condition (100% versus 110% versus 120% of the daily maintenance dose) was tested using Wilcoxon Signed Rank Test for each paired dose session (e.g. 100% versus 110%).

Summary

The studies in this thesis use a variety of different physiological measures. Clinical assessments of lung capacity are used to assess disease severity and treatment decisions; a relatively novel technique is used to measure electrical signals that are required for muscle contraction relative to capacity; blood gases are measured through different techniques which have all been described here. The chapter also described the subjective measures of drug effect, breathlessness and outlines the criteria that have been identified as respiratory depression. Without a standard measure of respiratory depression, there are various physiological measures and techniques that are required to be incorporated

5 Respiratory Depression and Underlying Respiratory Disease in a South London Drug Treatment Centre

5.1 Preface

This chapter explores the physiological and personal characteristic data from a sample of clients at a South London drug treatment centre. From January 2016 to January 2017, I had the opportunity to help assist my second supervisor Dr Caroline Jolley at the pop-up Lung Health Clinic at Lorraine Hewitt House. It was a great opportunity to observe the clinical application of a relatively novel health intervention and also to be able to recruit participants for the study described in this chapter.

For the study, I was involved in (and responsible for) the study design, participant recruitment as well as data collection and data analysis of this study. Study recruitment is by and large unpredictable and can be frustrating. This is particularly the case in a population where participation in research for some individuals is a less significant priority.

This chapter is divided into two parts; the first focusses on the descriptive and personal characteristic data of the opioid-dependent user (ODU) group; the second part of the chapter provides a comparative context to the ODU group data and delves into the novel area of respiratory disease and overdose risk crossover. Surprising though it may seem, the literature and general discussion of this crossover is relatively recent, and it has already proved important to guiding clinical practice and for paving the way to future research.

I presented some of the results of this chapter at the 2nd Lisbon Addictions conference in Portugal as well as at the 27th International Congress of the European Respiratory Society in Milan, Italy and the Society for the Study of Addiction conference in Newcastle, UK.

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5.2 Introduction

5.2.1 Background & Rationale

As described in chapter 3, opioids are mu-opioid receptor agonists with potent respiratory depressant properties. Opioids impact the control of breathing and cause fatal overdoses usually by respiratory failure as a consequence of a depressant and disruptive action on the regular breathing rhythm and respiratory drive. This can cause accumulation of high levels of carbon dioxide (hypercapnia) and low levels of oxygen (hypoxaemia) in the blood. A further complication of opioid overdose includes pulmonary oedema (Leino, Mildh, Lertola, Seppala, & Kirvela, 1999; Pattinson, 2008; White & Irvine, 1999). These opioid drugs act by binding to mu-opioid receptors which are present in the brain and brainstem respiratory centres. It has been shown that people on opioids (e.g. methadone or morphine) have a blunted ventilatory response to hypercapnia and hypoxaemia (Pattinson, 2008; Teichtahl et al., 2005; Weil et al., 1975).

The ability to take a breath depends on the balance between the load on the inspiratory muscles and their neuromuscular competence, i.e. their capacity. There is usually sufficient 'reserve' available to allow for any increase in load. Opioids suppress neural respiratory drive (NRD) and reduce the increase in NRD that would usually occur in response to an increase in respiratory load (Bailey et al., 2000; Bouillon et al., 2003; Brunton et al., 2008; Dahan, Aarts, & Smith, 2010; Ferguson & Drummond, 2006). Furthermore, respiratory depression by opioids involves dose-dependent responses of reduced tidal volume, bradypnoea (slowed rate of breathing), impaired pulmonary gas exchange and blunted responsiveness to hypoxia and hypercapnia (Pattinson, 2008). In order to compensate for changes to the load-capacity balance and to maintain adequate ventilation for blood gas homeostasis, NRD has to increase. If this does not occur, respiratory failure can occur. Respiratory failure is a syndrome in which the lungs fail in one or both of their two key functions; oxygenation and carbon dioxide elimination. Chapter 3 provides a more detailed explanation of the underlying basis for this.

In addition, there are a considerable number of risk factors that increase the risk of opioid overdose (see Chapter 3). With the exception of a recent study on acute effects on NRD and oxygen desaturation (Jolley et al., 2015b), there are no studies to date that have investigated the overlap between risk factors of overdose with novel physiological tools measuring markers of respiratory depression. Older age and male gender (Darke et al., 2006; Warner-Smith et al., 2001; Bartu et al., 2004), longer duration of drug use (Brugal et al., 2005; Hser et al., 2001) and previous experience of overdose (Tobin et al., 2005) and higher dose (Darke et al., 1999; McGregor et al., 1998; Desmond et al., 1978) are all considered to be risk factors that underlie opioid overdose. Polydrug use is possibly the most important risk factor in overdose deaths, with higher levels of polydrug use appearing to be associated with a higher risk of overdose, psychopathology and poor treatment outcome (Darke & Ross, 1997; DeMaria et al., 2000).

The data presented in this chapter allow examination of the relationship between opioid-induced respiratory depression signs and symptoms and overdose risk in opioid-dependent users. This observational study examined physiological parameters in individuals who were maintained on opioid substitution treatment for their heroin addiction. Recorded parameters were compared to those measured in corresponding non-opioid-using controls with no history of problematic drug or alcohol use, both with and without lung disease.

5.2.2 Aims & Hypotheses

The overarching aims and hypotheses of this chapter were:

Aim 1: to investigate the prevalence and severity of opioid-induced respiratory depression using specific respiratory depression criteria in long-term opioid-dependent users (ODU) and compare to corresponding non-opioid-using controls.

- Hypothesis 1: ODU participants experience more severe respiratory depression than corresponding opioid-naïve controls.

Aim 2: to examine the influence of personal, drug use and addiction treatment characteristics on the severity of respiratory depression.

- Hypothesis 2a: older age, male gender and a previous history of overdose are factors that are related to more severe respiratory depression.
- Hypothesis 2b: concurrent use of depressant drugs and injecting use of opioids are related to more severe respiratory depression.
- Hypothesis 2c: higher dose of Opioid Substitution Treatment (OST) is related to more severe respiratory depression.

Aim 3: to investigate the level of the NRD in ODU with particular focus on chronic obstructive lung disease compared to controls and whether there is an inappropriate suppression of NRD relative to the severity of lung disease.

- *Hypothesis 3:* levels of NRD in ODU participants with co-existing chronic obstructive lung disease are lower than opioid-naïve subjects matched for lung disease severity.

5.3 Methods

5.3.1 Ethical Approval

The study was approved by the King's College Hospital Research Ethics Committee (L/Rec reference number: 05/Q0703/82). It was conducted in accordance with the principles expressed in the Declaration of Helsinki. Written consent was provided by all participants prior to commencing the study.

5.3.2 Study Design

This was an observational study whereby the participant's medication and clinical treatment were not altered. The study group were seeking treatment for their heroin/opioid addiction and were recruited for this study as a convenience sample. Each participant attended one study session. Comparisons were made within-subject and between-subject. Screening was conducted prior to study visit by review of medical notes. All participants underwent spirometry (as described in the Methods section), earlobe blood gas test (to aid clinical determination of lung disease), urine drug screen (AllScreen) and alcohol breathalyser (BACtrack©) prior to the testing session; methods for this are described in the Methods chapter.

5.3.3 Setting

Recruitment and data collection for all participants within the study commenced in January 2016 and continued until April 2017. Participants were recruited from a South London Community Drug Treatment Centre (Lorraine Hewitt House). Potentially eligible participants were either approached through a regularly held Respiratory Clinic within the drug treatment clinic or through a researcher-led approach whilst the patient was in the waiting room. Testing was conducted at the Muscle Lab within King's College Hospital in a climate-controlled room maintained at 23 degrees centigrade. All study participants underwent screening before each study testing session.

5.3.4 Participants

All ODU participants were undergoing opioid maintenance treatment (e.g. methadone or buprenorphine). The following criteria were adhered to when selecting subjects:

Inclusion criteria:

1. Patients undergoing treatment for their opioid addiction, e.g. opioid substitution treatment such as methadone or buprenorphine or heroin maintenance treatment,
2. Age ≥ 18 years, no upper age limit,
3. Capable of providing voluntary informed written consent,
4. Clinician-determined diagnosis of an obstructive lung disease and no other potentially conflicting or impacting conditions (this is determined from clinical notes before the study and lung function results after the study).

Exclusion criteria:

1. Subjects suffering from severe respiratory insufficiency,
2. Current psychiatric diagnosis of major depression with suicidal ideation, psychosis, bipolar disorder, or any psychiatric disorder that would compromise the subject's ability to complete the study,
3. Female subjects who are pregnant or mothers who are lactating,
4. Any other factor that in the opinion of the investigators would make the subject unsafe or unsuitable for the study.

5.3.5 Control Participants

Controls corresponding to the ODU participants with lung disease (ODU-LD) were selected based on age, gender, BMI and lung function results. Control subjects were recruited from existing laboratory studies on lung disease. These patients had been recruited either from an outpatient respiratory clinic or through word of mouth. Control participants were selected on the basis of similarity to the study group, with regard to demographics and lung disease severity.

Healthy control participants (Healthy Controls) were eligible for inclusion if they were aged over 18 years old and had no history of respiratory, cardiac, neurological disease, or drug or alcohol addiction problems. Any subject with abnormal spirometry was excluded.

Lung disease control participants (Controls-LD) were eligible for inclusion if they were aged over 18 years old, had a clinician-determined diagnosis of a chronic, obstructive lung disease and no other potentially conflicting or impacting lung conditions such as bronchiectasis or lung cancer. Participants were excluded if they had co-diagnoses of cardiac or neurological disease as well as drug or alcohol addiction problems.

5.3.6 Outcomes and Measurement

All participants, of all groups, underwent a minimum total of 40 minutes of study testing (Table 5-1).

Table 5-1: Table of assessment, outcome, device and timing of each measure.

Assessment	Outcome Measurement	Device	Timing
Ventilation	Respiratory rate (Vf), tidal volume (VT) and minute ventilation (V_E)	Pneumotachograph	Total recording of minimum 10-mins with a break after 5mins
Pulse oximetry	Average and minimum SpO_2%	Finger-clip oximeter	Continuous recording for a minimum of 30-mins
End-tidal carbon dioxide	Average and maximum of peak %CO_2 per expired breath ($ETCO_2$%)	Adapted nasal cannula & capnograph	Recording for a minimum of 20-mins
Electromyography (parasternal intercostal muscles)	Neural Respiratory Drive: EMG_{para}a%max & EMG_{para}%index (see methods: (Murphy et al., 2011; Reilly et al., 2013; Reilly et al., 2011))	Surface electrodes and biomedical amplifier	Continuous recording for a minimum of 30-mins
Transcutaneous blood gas meter	Average and maximum $TcCO_2$	Ear lobe sensor	Continuous recording for a minimum of 30-mins

5.3.7 Neural Respiratory Drive

Neural Respiratory Drive (NRD) was determined using the parasternal electromyography methods described in Chapter 4. In brief, EMG_{para} was recorded transcutaneously using a bipolar pair of surface electrodes positioned bilaterally over the second intercostal space 3cm from the midline (Maarsingh et al., 2012; Murphy et al., 2011; Reilly et al., 2011). EMG_{para} signals were amplified and band-pass filtered between 10Hz and 2kHz and sampled at 4kHz. The raw EMG_{para} signal was converted to root mean square (RMS). The maximum RMS EMG_{para} per breath was determined and the mean peak EMG_{para} per breath for each recording block of interest was calculated. EMG_{para}%max was calculated by expressing mean peak RMS_{para} per breath as a percentage of the maximum RMS EMG_{para} recorded during maximal inspiratory manoeuvres (total lung capacity and inspiratory 'sniff' manoeuvres). EMG_{para}%max was multiplied by respiratory rate to derive the individual's Neural Respiratory Drive Index (NRDI) (Maarsingh et al., 2012; MacBean, Hughes, Nicol, Reilly, & Rafferty, 2016; Murphy et al., 2011; Reilly et al., 2011). More detailed description of the NRDI calculation is found in Chapter 4.

5.3.8 Capnography

Capnography was monitored by end-tidal and transcutaneous measures. All capnography data was measured and analysed as described in the Methods chapter. With regard to end-tidal carbon dioxide ($ETCO_2$), this is a measure of the concentration of carbon dioxide at the end of an exhaled breath and was measured using a Gas Analyser (iworx capnograph) in line with an adapted nasal cannula as described in Chapter 4. $ETCO_2$ was recorded as the peak percentage carbon dioxide (%CO_2) measured in each expired breath and converted to kPa. Transcutaneous carbon dioxide ($TcCO_2$) was measured using a transcutaneous capnograph (TOSCA TCM4, Radiometer Medical ApS, Brønshøj, Denmark) using an ear-clip sensor. The mean $TcCO_2$ level was calculated in mmHg and then converted to kPa. Further details on the methods can be found in Chapter 4.

5.3.9 Pulse Oximetry

Oxygen saturation (SpO_2) was recorded by finger pulse oximetry (Ohmeda Biox 3700) and by earlobe sensor (TOSCA). The pulse oximeter was calibrated as described in the Methods chapter. The oximeter recorded a percentage of blood oxygen saturation every 5 seconds. Recording started after attachment of the finger probe or ear-clip sensor on the participant. SpO_2 was continuously displayed in real time on the pulse oximeter and on LabChart and was stored for offline analysis.

5.3.10 Respiratory Flow and Volume Method

Participants were asked to tightly seal their lips around the mouthpiece of the pneumotachograph (attached to a Validyne and to Powerlab). Airflow during relaxed, resting breathing was recorded over a minimum of 10 minutes with a short break after 5 minutes. A noseclip was in place throughout. Recording was continuously displayed on LabChart in real time and stored for offline analysis. More detailed description of this is in Chapter 4.

5.3.11 Breathlessness scale

Breathlessness was measured using the modified MRC (mMRC) dyspnoea scale. There are four grades of breathlessness that individuals can experience, ranging from 0 to 4; these are highlighted in more detail in the Methods chapter.

5.3.12 Personal, Drug Use and Addiction Treatment Characteristics

Characteristics relating to personal, drug use or wider behavioural or addiction treatment related factors were obtained through a detailed medical history questionnaire at the start of the study session. These were asked by me or my supervisor Dr Caroline Jolley. These questions can be found in the appendix (C-8).

5.3.13 Indicators of Respiratory Depression

Physiological measures were represented as absolute values and also, the presence and frequency of pre-defined respiratory depression criteria (more details below). Evidence of significant respiratory depression was recorded using a variety of physiological markers. Criteria and threshold levels are indicative of clinically-significant respiratory depression and were determined through Sleep Medicine and Anaesthesiology literature (Dahan et al., 2010; Douglas, 2005) and through discussions and advice from members of the respiratory medicine research group which included critical care consultants, respiratory medicine consultants, and other allied experts as well as academic supervisors and co-investigators.

Overall, four main measures were used to capture respiratory depression. Further, any presence of, or frequencies pertaining to, these physiological markers were used to establish the existence of significant respiratory depression:

1. End-tidal carbon dioxide ($ETCO_2$)
    a) Absolute value (kPa),
    b) $ETCO_2$ > 6.6kPa per breath,
    c) Frequency of breaths above 6.6kPa.
2. Neural Respiratory Drive (NRD) and Airflow
    a) NRD index (NRDI) value (min^{-1}), normalised against respiratory rate and maximal manoeuvres as above (Section 5.3.6),

b) Any presence of NRD pauses or absence of inspiratory airflow of longer than 10 seconds (apnoea),

c) Frequency of pauses of longer than 10 seconds.

3. Transcutaneous carbon dioxide ($TcCO_2$)

a) Absolute value (kPa),

b) Overall average above 6kPa across the study session.

4. Oxygen saturation (SpO_2)

a) SpO_2 (%),

b) Any presence of SpO_2 below 90% for longer than 10 seconds.

c) Frequency of dips below 90% for longer than 10 seconds.

For each criterion, the actual values of each measure were initially recorded, and subsequently a dichotomous categorisation (e.g. any presence of a breath above 6.6kPa) as well as frequencies of each criteria (e.g. number of breaths above 6.6kPa in the whole session) were determined, with the except for $TcCO_2$ where the marker was represented as a mean of the whole measurement. The absolute values of the measures along with categorised and frequency data were used to determine Aim 1. Aim 2 was analysed with the measures and frequency data to create a series of respiratory depression criteria against which each personal- and drug use-related characteristic was tested. Finally, Aim 3 was analysed using the measures of NRD along with each of the other physiological measurements.

5.3.14 Study Size

As a physiological study of n=20 (with equal n=20 corresponding controls), the sample size was considered sufficient to reflect variations in the population of interest, and also to allow for intensive study methods. Studies of this type have typically used sample sizes close to this number by utilising design of repeated measures with the same subjects, thereby obtaining strength from within-subject study design (Jolley et al., 2015b; Lintzeris et al., 2007; Reilly et al., 2011).

5.3.15 Statistical Methods

Where appropriate, data were tested for normality. Any ordinal data were presented as median (interquartile range) and non-parametric bivariate testing was used. Dichotomous 2x2 criteria or categorical data between groups were tested using Fisher's exact test or Pearson's Chi Square. Spearman Rank (Rs) was used to assess frequency data and the relationship between related continuous, scale data and also, Mann Whitney U (U-statistic) were used to test for differences between groups. Categorical data such as gender, smoking status and type of drug were compared only with the categorical physiological data, i.e. to whether there was any presence of certain physiological indices. Data analyses were performed using SPSS software v22 for Mac (SPSS Inc, Chicago, Illinois, USA). Significance was determined at values of $p < 0.05$ level or at $p < 0.01$.

5.3.16 Opioid Substitution Treatment (OST) Dose Comparison

Direct equivalent dose comparisons are difficult to attain for opioids. The comparisons are not exact conversions but are there as general guide to equivalence in order to allow comparison of doses between subjects. It is particularly difficult to compare doses above 80mg methadone and 16mg buprenorphine, which applies to three participants in this study. The Defined Daily Dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication and does not necessarily represent the recommended daily dose. It can be used as an estimate of consumption in a fixed unit of measurement, independent of price and formulation and is useful when comparing different opioids together (Strang, Hall, Hickman, & Bird, 2010; WHO, 2012). The calculation is: Drug usage (in DDDs) = items issued x amount of drug per item / DDD.

All Opioid Substitution Treatment (OST) doses in this study were calculated according to this DDD for a given opioid. For example, for methadone the daily dose is 60mg and for buprenorphine it is 8mg because these are close to the average dose prescribed in the UK (BNF, 2018; H. E. Jones et al., 2007; NAABT, 2007) and are on the lower point of the recommended dose ranges. Thus, if a participant is on 60mg methadone, they would be assigned '1 DDD'.

5.4 Results

The results are broken down into three subsections; firstly, I provide an overview of the general features of the opioid-dependent group, followed by the second part of the results focussing on respiratory function tests and wider personal and behavioural characteristics. The third part of the results focusses on comparison of the physiological results to controls.

5.5 Part one: Overview of the Group

5.5.1 Descriptive Data

All participants completed the full duration of testing, however, in three sessions, the length of time was extended due to speech, movement or laughter which causes artefact on the measurement signals. Out of the 37 that were eligible for the study, 22 people were studied in full but 20 of these were considered acceptable and further analysed. Two datasets were rejected; one because of measurement artefact and the second because of the presence of restrictive lung disease. The total number of individuals who were recruited for the study as well as the number of drop-outs and reasons for these drop-outs are all stated in the flowchart (Figure 5-1).

Twenty control subjects undertook the same protocol as the ODU participants. Thirteen control participants with obstructive lung disease were recruited for comparison with the ODU-LD group, and seven matched healthy controls corresponded to the seven ODUs with no lung disease. Demographics, anthropometrics and lung function results are highlighted in (Table 5-2). Significant differences were observed in the level of NRDI amongst the two control groups (Figure 5-5; $p=0.001$).

Anthropometric, demographic and basic lung function and physiological data are represented for all participants of the study in Table 5-2 and Table 5-4 (and comparisons in Table 5-3) and full individual results for ODU participants are provided in Appendix C. The ODU group included four female and 16 male participants, with a median (IQR) Body Mass Index (BMI) of 26.5 (21.8-30.4) kg/m^2. The median (IQR) age was 49 years old (44-55 years old). The median (IQR) age of first heroin use was 20 years old (18-27 years old), and the median (IQR) age of first entrance into treatment for heroin addiction was 33 (24-40 years old). The median (IQR) duration of drug use was 27 years (19-32 years). Eleven participants of the 20 reported to have previously experienced an opioid overdose that required hospitalisation and/or reversal by naloxone. Twelve participants were prescribed buprenorphine or suboxone (two of whom took their dose via the sublingual route, the remaining via oral route), six were prescribed methadone (one of which was injectable), one was prescribed injectable diamorphine and one was prescribed oral diamorphine. With regard to cigarette smoking, three participants were ex-smokers, and the remaining 17 were current, and overall the median (IQR) smoking history was 15 (10-25) pack years. Eight of the 20 participants had taken their opioid substitution treatment on the day of testing. The majority (12) were prescribed buprenorphine or suboxone as part of their opiate maintenance treatment, and of these, eight had previously been in treatment on methadone. Two participants took their OST via injectable route (diamorphine and methadone), two others via sublingual route (buprenorphine), and the rest via oral route.

Lung function measures varied greatly and two distinct groups within the opioid-dependent users were established: ODUs with no lung disease (ODU), and ODUs with lung disease (ODU-LD). The subsequent data will be presented with these distinct groups. Of the 20 opioid-dependent users, 13 had obstructive lung disease by lung function and clinical criteria. Of these, only five had previously been diagnosed with a chronic lung disease and had been prescribed appropriate medication. The following medication (other than OST) was used by the participants: 5 benzodiazepines (temazepam, diazepam and alprazolam), 4 long-acting, anticholinergic bronchodilator (Tiotropium), 4 anti-psychotic, 3 anti-depressants (SSRIs & atypical), 2 short-acting β-agonist inhalers, 1 antiviral medication for hepatitis C and 1 other was on a calcium channel blocker.

Over half (55%) of ODU participants were not troubled by breathlessness as measured by the mMRC Dyspnoea Scale, and seven experienced shortness of breath when hurrying or going up a slight hill (mMRC grade 1 dyspnoea). Two ODU participants experienced moderate to severe breathlessness where they felt slower than people their own age (because of breathlessness) (grade 2) or where they had to stop for breaths after a few minutes of walking (grade 3). All participants completed the full duration of testing, however, in three sessions, the length of time was extended due to speech, movement or laughter which causes artefact on the measurement signals.

5.5.2 Other Drug Use

Fifteen of the 20 ODU participants self-reported use of other drugs and/or alcohol. Seven participants reported using alcohol at quantities above the weekly recommended allowance (14 units). Six reported using cannabis, three of which were daily users. Five participants reported using benzodiazepines, two of which also reported high quantities of alcohol use. Dipstick urine drug screening showed presence of drugs in all except five cases. There were no notable differences in the physiological responses between these five cases compared to other participants who showed presence of a drug. The most commonly detected metabolites in the urine dipstick test were morphine (10) and methadone (eight). A positive alcohol breathalyser was detected in two of the 20 participants; their percentage blood alcohol content (BAC) measurements were 0.17% and 0.0026%.

Results by individual ODU can be seen in Appendix C-1, C-2 and C-3.

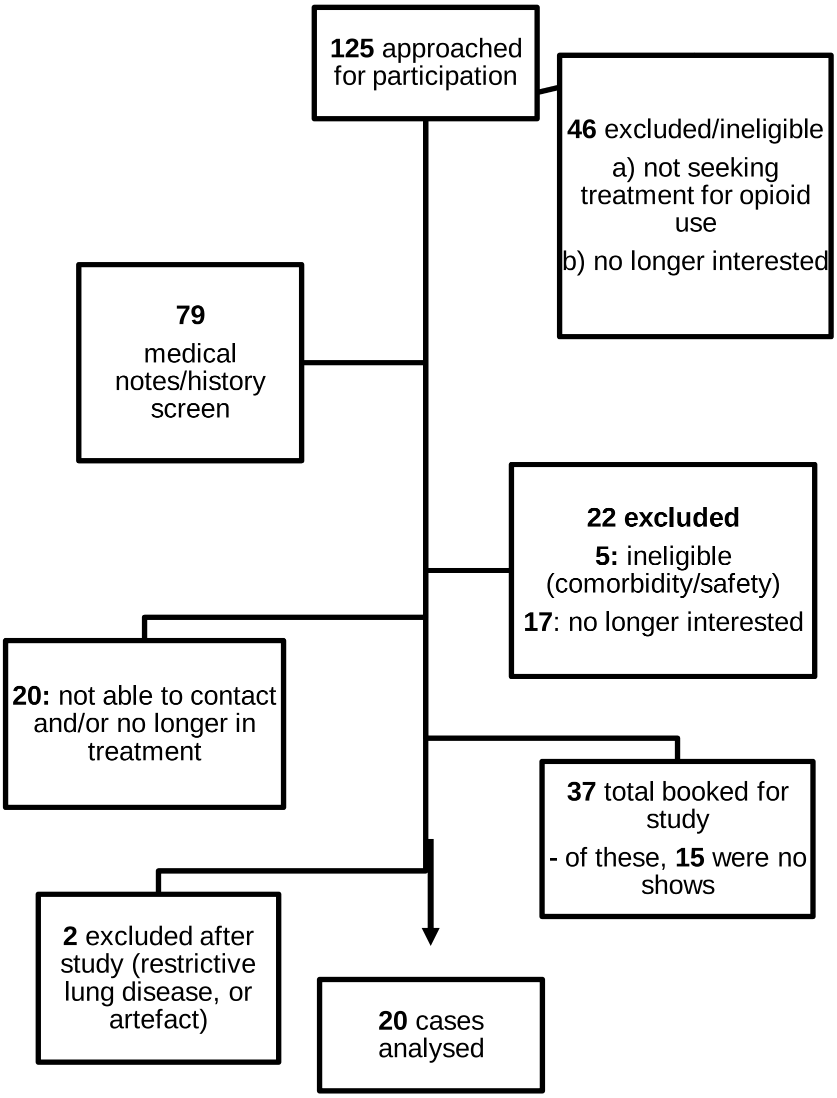

Figure 5-1: flowchart of the number of individuals that were recruited for the opioid user group at each recruitment stage.

Table 5-2: Demographics and lung function results for all four groups. FEV_1%pred: % predicted of Forced Expiratory Volume in 1 second; VC%pred: % predicted of Vital Capacity .

All Groups		Age (years)	BMI (kg/m^2)	FEV_1%pred (%)	VC%pred (%)	FEV_1/VC%ratio (%)	Gender (F/M)
ODU (n=7)	**Median**	48	30.0	96.1	99.7	74.7	2/5
	IQR	46 - 52	27.2–32.1	90.5–96.5	96.9–107.1	71.9 – 76.8	
Healthy Controls (n=7)	**Median**	50	26	100	108.1	75	1/6
	IQR	44.5-56.5	23.9-26.6	97.5-110.3	99.6-115.1	69.7-78.5	
ODU-LD (n=13)	**Median**	49	23	77.1	106.7	60.2	2/11
	IQR	42-55	19.7-28	66.8-90.1	96-114.8	48.7-64.3	
Controls-LD (n=13)	**Median**	66	27	60	104.6	52	3/10
	IQR	62-72	24.3-30	52.8-74.5	85.4-111.6	45-56.6	
Total (n=40)	**Median**	**49**	**26.5**	**82.9**	**105.5**	**62.9**	**8/32**
	IQR	**44.3-55**	**21.8-30.4**	**60.1-96.1**	**93.1-114.6**	**50.7-74.7**	

Table 5-3: Between-group comparisons of lung function results and demographics of ODU-LD and their corresponding controls (top) and ODU without lung disease and their corresponding controls (bottom).
ODU-LD and their controls were matched in all criteria except age (n=13 in each group), ODU without lung disease and their controls were matched in all criteria (n=7 in each group).

	Age	BMI	FEV_1%pred.	VC%pred.	FEV_1/VC%pred.	Gender
			ODU and Controls:			
U-Statistic (p value)	18.5 (0.44)	11 (0.90)	12 (0.11)	16 (0.28)	23 (0.85)	21 (0.53)
			ODU-LD and Controls-LD:			
U-statistic (p value)	16.5 (0.0001)	69.5 (0.44)	51.5 (0.90)	67 (0.37)	62 (0.25)	78 (0.63)

5.6 Part Two: Results of Testing of Respiratory Function

5.6.1 Prevalence and Severity of Respiratory Depression Amongst ODUs (Aim 1)

At least one of the respiratory depression indicators was observed by all of the 20 participants and at least two of these indicators were observed in over half (11) (Table 5-6). The overall median (IQR) of SpO_2% was 95.6% (94.0-96.8%) and the median (IQR) peak $ETCO_2$ per breath was 5.8kPa (5.4-6.4kPa); the $TcCO_2$ median (IQR) was 5.8kPa (5.0-6.2kPa). SpO_2% was generally in the normal expected ranges, despite marked high levels observed in some of the participants' capnography ($ETCO_2$% and $TcCO_2$) recordings (Table 5-4).

Of the seven ODUs with no identified lung disease, five showed at least two indicators of respiratory depression. Of the ODU-LD participants, six showed at least two indicators of respiratory depression. Between the two ODU groups, there were no differences in severity of respiratory depression or NRDI (X_2 1.7, p=0.19).

A wide range of severity was observed with some participants displaying more severe physiological responses than others. In one ODU an apnoeic frequency of 1 pause per minute was observed. A sample of this is shown in Figure 5-2 with a comparison sample from an individual with a regular pattern of breathing and no opioid dependency.

5.6.2 Individual and Wider Behavioural Features (Aim 2)

Age was inversely correlated with NRDI (Rs= -0.43, p= 0.04); and smoking pack year history (Rs= -0.42, p=0.045) was inversely correlated with levels of SpO_2% but there was no correlation with the measures of diffusing or transfer capacity of carbon monoxide, KCOc and TLCOc (Appendix: C-5). Gender, smoking status and BMI did not show any relationship with any of the physiological measures (Table 5-5).

5.6.3 Features of Drug Use (Aim 2)

The number of previous overdose events was correlated to $ETCO_2$ (Rs= 0.42, p=0.04). Duration of overall drug use showed a significant relationship with $TcCO_2$ (Rs= 0.45, p=0.04), frequency of NRDI pauses (Rs= 0.51, p=0.02) as well as an inverse relationship with NRDI

(Rs= -0.44, p=0.05 (Table 5-5). Other features of drug use measured in this study did not show any relationship with the respiratory depression criteria. These included route of previous opioid use, OST consumption on the study day and co-use of other drugs.

5.6.4 Features of Addiction Treatment (Aim 2)

OST dose was correlated to $ETCO_2$ (Rs= 0.57, p=0.009), $ETCO_2$ frequency (Rs= 0.57, p=0.008) and frequency of NRDI pauses (Rs= 0.47, p=0.04). No other feature of addiction treatment, namely the type of OST, number of times in any type of opioid addiction treatment, the number of months in current treatment and the dosing regimen, was associated with physiological measures of respiratory depression (Table 5-5).

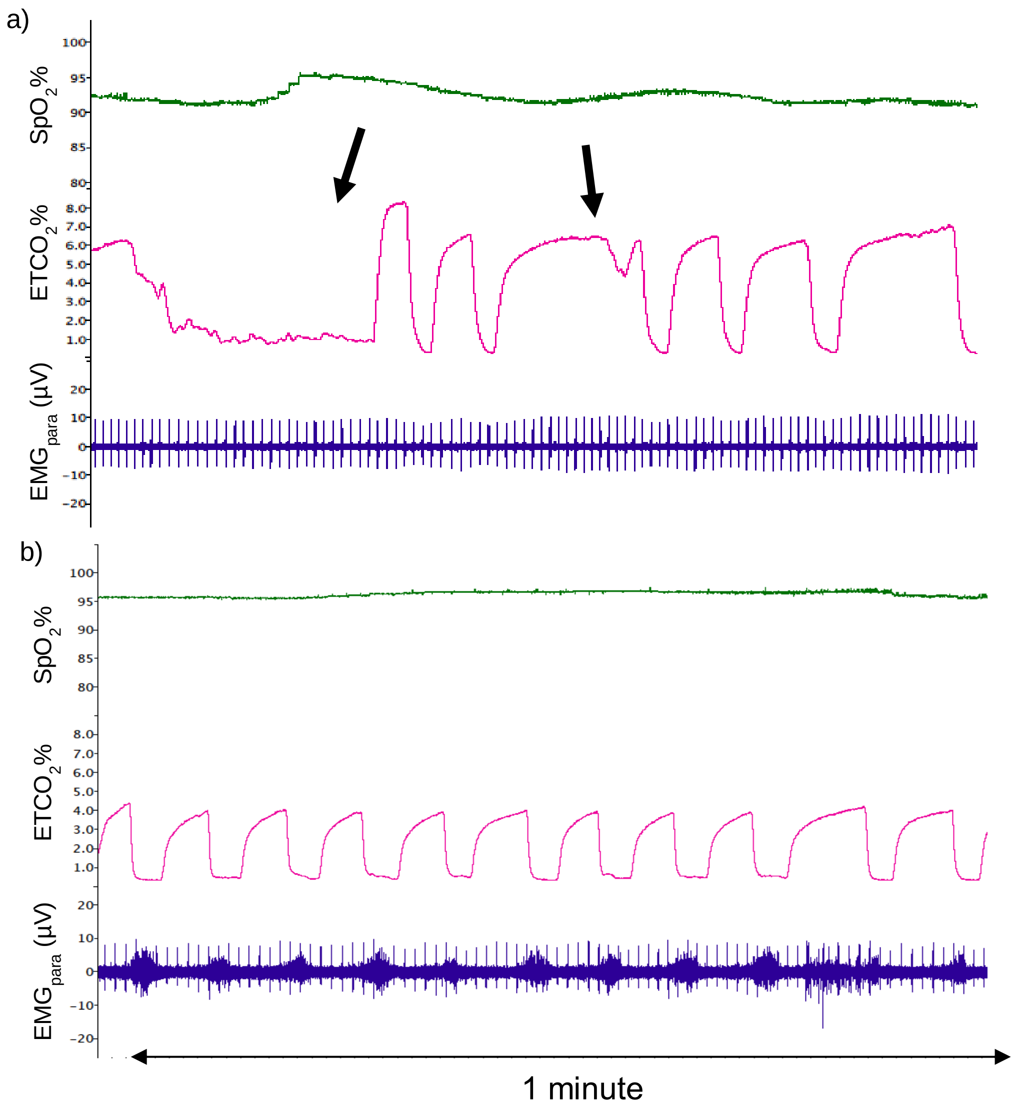

Figure 5-2: Sample of signal recording in two separate individuals.
a) Opioid Dependent User with Lung Disease (ODU-LD); b) Lung disease control. Measurements shown are: SpO_2%, $ETCO_2$%, EMG_{para} (µV), respectively. ODU-LD individual displays two respiratory pauses (apnoeic episodes) of 12 and 10 seconds (black arrows), respectively, within this 1-minute period, compared to regular pattern of breathing in the control. Similar severity of lung disease existed between both participants (FEV_1%pred: 65.6% for LD-control and 66.8% for ODU-LD).

Table 5-4 a and b: Physiological measures (separated by a) blood gases & drive and b) ventilatory function) for all groups. Opioid-Dependent Users with no lung disease (ODU), their corresponding controls (Controls), Opioid-Dependent Users with Lung Disease (ODU-LD), Controls with Lung Disease (Controls-LD). The bottom rows display all controls and all ODU. *Significant difference between medians, *p<0.05; **p<0.01, which was seen only between ODU-LD and Controls-LD in $ETCO_2$, $TcCO_2$ and NRDI (U-statistic: 19, 44 and 30, respectively).

Table 5-4 a) Blood Gases and neural respiratory drive:

		SpO_2 (%)			$ETCO_2$ (kPa)			$TcCO_2$ (kPa)			NRDI (min^{-1})		
		Median	Min	Max	Median	Min	Max	Median	Min	Max	Median	Min	Max
Groups	**ODU**	95.85	93.90	98.53	5.93	5.18	6.48	5.77	4.67	6.75	87.62	51.67	115.30
	Controls	96.33	95.00	98.01	5.79	5.52	6.31	5.51	4.10	5.99	76.93	52.80	164.20
	ODU-LD	95.30	91.80	98.30	**5.80****	4.58	7.15	**5.68***	4.39	7.35	**148.51****	34.99	172.62
	Controls-LD	93.80	89.44	95.90	**4.58****	3.56	5.50	**5.00***	3.46	6.10	**217.02****	43.70	504.50
All	**ODU**	96.22	93.90	98.53	5.84	5.18	6.48	5.68	4.10	6.75	79.69	51.67	164.20
All	**Controls**	94.29	89.44	98.30	5.24	3.56	7.15	5.22	3.46	7.35	158.92	34.99	504.50

Table 5-4 b) Ventilatory Function

		Respiratory Rate (breaths/min)			Tidal Volume, VT (L)			Minute ventilation, V_E (L/min)		
		Median	Min	Max	Median	Min	Max	Median	Min	Max
Groups	**ODU**	13.20	10.00	18.10	0.8	0.3	1.0	11.4	5.6	14.1
	Controls	13.00	6.00	16.20	1.0	0.6	1.5	12.1	8.7	19.0
	ODU-LD	13.60	6.60	15.50	0.7	0.1	1.9	9.2	1.9	18.0
	Controls-LD	15.47	7.00	25.71	0.9	0.3	1.8	12.3	4.9	18.7
All	**ODU**	13.60	6.00	18.10	0.74	0.13	1.88	9.52	1.91	17.95
All	**Controls**	13.99	6.60	25.71	1.0	0.28	1.76	12.10	4.88	18.96

Table 5-5: Results of bivariate correlation (Rs) for personal and wider behaviour, drug use and opioid addiction treatment factors underlying risk of opioid overdose. *p<0.05, **p<0.01

Characteristic	$ETCO_2$ (kPa)	$ETCO_2$ >6.6kPa freq.	NRDI (min^{-1})	Resp pauses >10s freq.	$TcCO_2$ (kPa)	SpO_2 (%)	SpO_2 < 90% >10s frequency
Age	-0.30	-0.32	**-0.43***	-0.08	0.28	-0.28	0.17
BMI	0.28	0.12	-0.10	0.22	-0.08	-0.30	0.37
Smoking pack history	-0.36	-0.30	0.17	0.03	0.17	**-0.41***	0.28
Duration of Drug Use	0.15	-0.14	-0.44*	0.51*	0.47*	-0.04	0.06
No. previous OD events	**0.42***	0.17	-0.16	0.23	0.14	0.13	-0.04
OST dose	**0.57****	**0.57****	-0.13	**0.47***	-0.09	0.07	-0.03
No. opioid addiction Tx	0.02	0.05	-0.26	-0.28	0.05	-0.07	0.17
No. months on current dose	-0.07	0.03	0.002	-0.007	-0.05	0.19	-0.32

Table 5-6: Table displaying presence of respiratory depression criteria in all ODU and their corresponding controls.
Fisher's exact test was used to test for differences between criteria, both groups showed significant differences. ODU and controls p=0.021, and ODU-LD and Controls-LD p=0.0001.

Number	SpO_2 <90% >10s	$ETCO_2$ breaths >6.6kPa	$TcCO_2$ >6kPa mean	Resp Pauses >10s	Number	SpO_2 <90% >10s	$ETCO_2$ breaths >6.6kPa	$TcCO_2$ >6kPa mean	Resp Pauses >10s
ODU (healthy):					**Controls (healthy):**				
1		✓		✓	1		✓		
2		✓	✓	✓	2		✓		
5	✓			✓	3				
8			✓	✓	4				
9		✓	✓		5				
16		✓			6				
18		✓		✓	7				
ODU-LD:					**Controls-LD:**				
3			✓		1				
4		✓			2				
6	✓	✓		✓	3				
7			✓		4				
10	✓		✓		5				
11	✓	✓		✓	6				
12		✓			7				
13		✓			8				
14	✓	✓	✓	✓	9		✓		
15				✓	10		✓		
17		✓	✓	✓	11				
19		✓		✓	12				
20		✓			13				

Table 5-7: Comparison of severity of respiratory depression indices for all ODU participants and their corresponding controls.
The average (range) number of indices/criteria exhibited by participants across 20 minutes of testing is shown, as well as U-statistic (p value) between the groups. Significant differences (Mann Whitney U test: U-statistic (p value)) between ODUs and controls were observed in both sets of groups across all respiratory depression criteria except SpO_2. *p<0.05; **p<0.01.

Respiratory Depression Indices:	Opioid-Dependent User n=7	Healthy Controls n=7	Opioid-Dependent User, Lung Disease n=13	Lung Disease Controls n=13
SpO_2 dips	0.5 (0-3)	None	1.6 (0-16)	None
U-statistic (p value)	17.5 (0.28)		58.5 (0.03*)	
$ETCO_2$ increases	31.6 (0-200)	0.3 (0-2)	66.1 (0-280)	0.3 (0-3)
U-statistic (p value)	10 (0.04*)		30 (0.002**)	
Resp. pauses	1.6 (0-4)	0	2.5 (0-20)	0
U-statistic (p value)	7 (0.009**)		45.5 (0.007**)	

5.7 Part Three: Comparison to controls

The next part of this chapter focuses on the comparison of the ODU group to relevant related controls.

5.7.1 Severity of Respiratory Depression Amongst ODU Compared to Controls (Aim 1)

Controls were correlated based on age, BMI, gender and lung function values, smoking status (Table 5-3). Of the control group with no lung disease (i.e. healthy controls), only two participants observed one indicator of respiratory depression. A significant difference in the frequency of respiratory depression indicators was observed between the two groups (Table 5-6; p=0.021). With regard to differences between the two groups for each criterion, all except SpO_2% was significantly different (Table 5-7).

All characteristics except age were significantly similar to the study group (Table 5-3). Only two participants in the control group showed an indicator of significant respiratory depression. Overall, the difference between frequencies was significant (Table 5-6; p=0.0001). For each criterion, the differences between frequencies of criteria were also significant compared to controls (Table 5-7).

Overall, in comparison to control participants, there was a greater frequency of significant respiratory depression in all ODU than in all controls, across all groups (p=0.021, Fisher's exact test). Furthermore, there were also significant differences between $ETCO_2$, $TcCO_2$ and NRDI between the ODU-LD and lung disease controls (Table 5-4).

5.7.2 Level of NRDI in ODU with Lung Disease (Aim 3)

Thirteen ODU-LD participants were compared with 13 controls with lung disease (Tables 5-4, 5-6 & 5-7). ODU participants with moderate to severe COPD were compared to similar participants with the same severity of lung disease. NRD was observed to be significantly lower in the ODU-LD group compared to lung disease controls (Figures 5-3 & 5-6). None of the ODU-LD participants had a NRDI higher than 173min^{-1}.

There was no statistically significant correlation between FEV_1%pred and NRDI in ODU-LD (Rs=0.43, p=0.14) but a non-significant trend towards an inverse relationship with FEV_1%pred and NRDI in lung disease controls (Rs= -0.41, p=0.14) (Figure 5-4 & Table 5-8). Amongst the same two groups, there was no statistically significant relationship between NRDI and $ETCO_2$ (Rs= -0.19, p=0.5), $TcCO_2$ (Rs=-0.19, p=0.7) and SpO_2 (Table 5-8).

Amongst ODU without lung disease and relevant control group, there was no statistically significant correlation between NRDI and $ETCO_2$ (Rs=-0.57 and p=0.49) but there was no relationship between NRDI and $ETCO_2$ (Rs = 0.089, p=0.8), $TcCO_2$ and SpO_2 (Table 5-8).

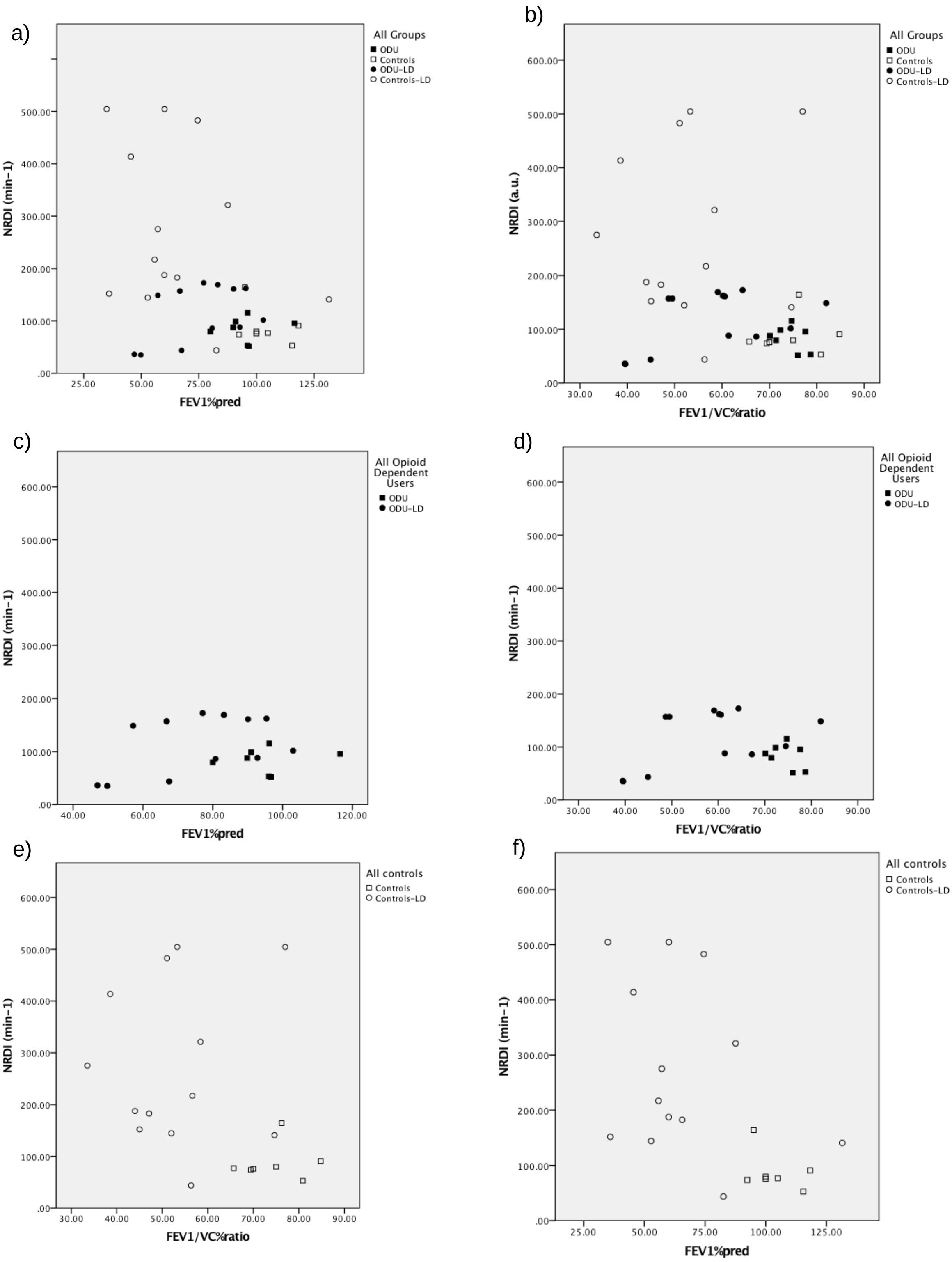

Figure 5-3a-f: Scatterplots of lung function measures of FEV_1%pred and the FEV_1/VC%ratio against the normalised index of Neural Respiratory Drive (NRDI). a) all groups, FEV_1%pred; b) all groups, FEV_1/VC%ratio; c) all ODU and ODU-LD, FEV_1%pred; d) all ODU and ODU-LD, FEV_1/VC%ratio; e) all controls, FEV_1%pred; f) all controls, FEV_1/VC%ratio.

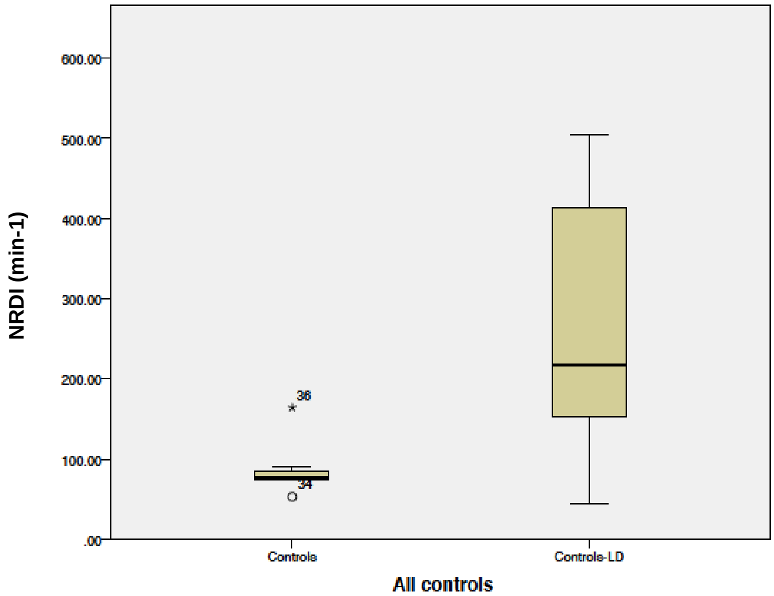

Figure 5-4: Boxplot of NRDI values for healthy control and lung disease control (U= 10, p=0.005).

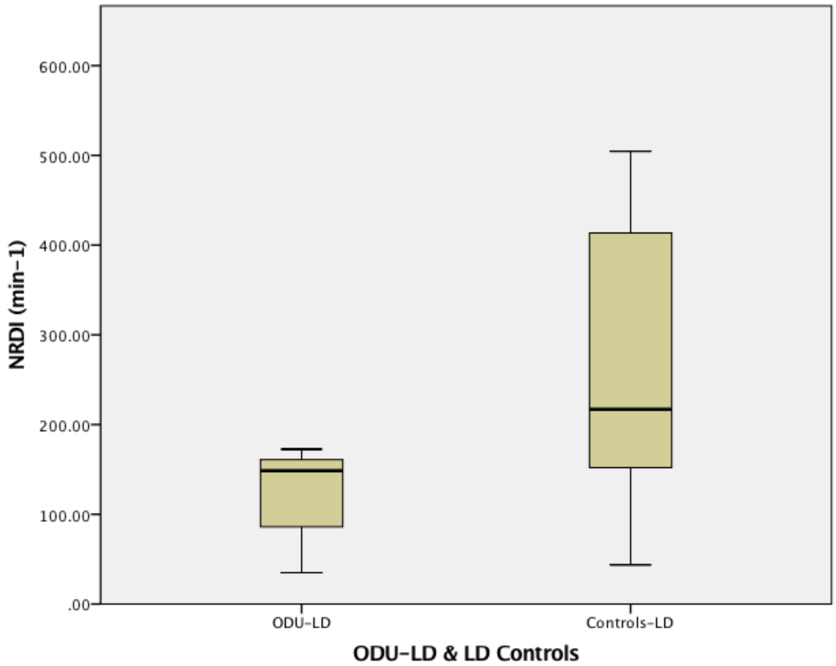

Figure 5-5: box plot of the NRDI of the ODU versus control group. (U= 30, p=0.005).

Table 5-8: Table showing correlations coefficients, Rs (p value) of each blood gas and lung function measure against NRDI. Corresponding scatterplots in Figure 5-4.

	ODU	Controls	ODU-LD	LD Controls
$ETCO_2$ average peak per breath against NRDi	0.07 (0.89)	-0.57 (0.18)	-0.19 (0.54)	0.49 (0.08)
SpO_2 average against NRDI	-0.14 (0.79)	0.29 (0.54)	0.25 (0.42)	-0.33 (0.29)
$TcCO_2$ average against NRDI	-0.32 (0.48)	-0.36 (0.43)	0.027 (0.93)	0.26 (0.39)
FEV_1%pred against NRDI	0.04 (0.94)	0	0.43 (0.14)	-0.41 (0.16)
FEV_1/VC% against NRDI	-0.25 (0.59)	0.29 (0.53)	0.35 (0.25)	0.12 (0.69)

5.8 Discussion

5.8.1 Summary of Principal Findings

The results of this study demonstrate that everyday respiratory depression is habitually present in opioid dependent users and is significantly more severe than related opioid-naïve controls. Furthermore, the results also show that certain personal, wider behavioural, treatment and drug use factors are related to chronic respiratory depression. In addition, the results also show that NRD appears to be significantly lower than that of controls in ODU with lung disease compared to non-ODU controls with lung disease.

5.8.2 Respiratory Depression Indices in ODU

It is important to acknowledge at the onset that there is no standard measure of respiratory depression. However, the criteria used in this study are widely accepted indices of respiratory depression, encompassing different aspects of the condition. Additionally, it has now been shown that, using continuous, advanced monitoring techniques, it is possible to detect opioid-induced respiratory depression (Gerdung et al., 2016; Gupta & Edwards, 2018; Jolley et al., 2015b). These criteria were observed to be consistently present throughout the study in ODU. Respiratory depression indices were significantly more frequently observed in both ODU groups compared to their corresponding controls. In fact, in some cases it was particularly severe, where apnoeas and peak $ETCO_2$ per breath reached levels approaching thresholds that would be considered near-life-threatening under usual clinical circumstances in non-opioid using individuals. The study presented in this chapter applied these techniques within an opioid-using population in a setting that aimed to capture realistic everyday physiological functioning. However, the question of whether attaining these criteria provides a clear indication of fatal or non-fatal overdose risk is to be discussed in the rest of this section. Nevertheless, the data presented in this chapter allow for further study and provide unique exploratory data to build upon. It is crucial to further study the health impact of this chronic respiratory depression.

5.8.3 Personal and Wider Behaviour Characteristics

Some of the personal, treatment and medical features showed significant relationships with one or more of the respiratory depression markers. Male gender was not correlated to more severe respiratory depression. However, it must be noted that the number of female participants was particularly low in this study, and there may be other factors, outside the scope of this thesis, that lead to more males experiencing overdoses. Age was found to be inversely associated with NRDI, indicating that NRDI may be decreasing with age in ODU. There are differing findings in the literature, with variable suggestion that age may not significantly change at rest or may increase with older age (Jolley et al., 2015a, 2009). Others show that there might also be an inverse trend (MacBean, Hughes, Nicol, Reilly, & Rafferty, 2016; Pollock et al., 2015). Chronic opioid use amongst older people is an issue that has raised much attention in recent years (Gao et al., 2016; RCPsych, 2011). With regard to data on physiological responses to opioids presented in this chapter, these data do not appear to show that age was related to more severe respiratory depression. As the youngest participants were not aged below 37 years old, with only four participants in their 30s, there are obvious difficulties in generalising these data. A greater and more varied sample size is required to test these findings further. There is more detailed discussion of age in connection to methadone users later on in this chapter.

A higher smoking pack year history was related to lower levels of SpO_2%. It is unclear whether this is in connection with current or recent use of cigarettes/tobacco or to the potential longer-term effects of smoking. Pulse oximeters are not able to differentiate between carboxy-haemoglobin and oxy-haemoglobin (Hampson, 1998) and so, often SpO_2% records as normal even where there is a higher presence of carbon monoxide in the bloodstream of smokers, however, the literature on this seems unclear (Glass, Dillard, Phillips, Torrington, & Thompson, 1996). Previous studies have shown that smoking does not have a relationship with lower SpO_2 values or changes in mean (Kline, Nelson, Jackson, & Courtney, 2002; Witting & Scharf, 2008). The effects of long term cigarette smoking in relation to this population are probably most crucial to the increased risk of chronic respiratory diseases (ONS, 2016). However, there was no correlation with smoking pack history and the measures of diffusing and transfer capacity of carbon monoxide, KCO_c or $TLCO_c$ (using true values and predicted values, Appendix: C5). These values reflect the efficiency of gaseous diffusion across the alveolar-capillary gas exchange interface. Changes to these values represent the signs of COPD progression, particularly for emphysema patients. In emphysema, there is a loss of alveoli and capillary bed which results in a lower surface area available for gaseous diffusion and a decrease in TLCO (Bailey, 2012; Owens, Rogers, Pennock, & Levin, 1984).

5.8.4 Drug Use Characteristics

The number of previous overdose events and the duration of drug use were associated with the two measures of carbon dioxide, $ETCO_2$ and $TcCO_2$. Both factors showed that the greater the overdose events, and the longer the period of drug use, the higher the levels of $ETCO_2$ and $TcCO_2$. Hypercapnia is caused by alveolar hypoventilation and is a common effect of opioids. Further, the duration of drug use, similar to age, also showed an inverse association with NRDI and a positive correlation with the number of apnoeic pauses (lasting longer than 10 seconds) and the high level of $TcCO_2$. Thus, the longer the duration of use, the more episodes of respiratory depression were observed. Duration of drug use reported in this study did not take into account any periods of entry into drug treatment; it is a general measure of years of opioid use. Nonetheless, these results showed that there was a dampened level of drive, an increase in apnoeic pauses, and a higher level of carbon dioxide with a longer duration of treatment. It is certainly the case that an occurrence of these in combination is potentially fatal.

5.8.5 Treatment Characteristics

A higher dose of OST medication was associated with higher levels of $ETCO_2$, greater number of $ETCO_2$ breaths above 6.6kPa as well as a higher number of apnoeic pauses. It has been well-established that methadone and other opioid substitution treatments reduce the risk of all cause, and overdose, mortality, in some cases by a factor of 3-4 in opioid drug users (Degenhardt et al., 2009; NIH, 1998; Sordo et al., 2017). While it might be unsurprising that a higher dose of OST would be associated with higher levels of the stated criteria, it is interesting that this would occur in tolerant opioid users. It has been shown that the initial period of one to four weeks of drug treatment is associated with a higher rate of mortality (Cornish, Macleod, Strang, Vickerman, & Hickman, 2010). Participants in this study had been in treatment for at least four weeks, but it would be interesting to investigate whether there is a similar association amongst individuals who are in the first few weeks of treatment.

Contrary to hypotheses, the duration of current treatment was not associated with any of the respiratory depression criteria. There was a large variability with the distribution of duration of current treatment, ranging from one to 168 months (with a median and IQR of 12 months and 2.5 to 51 months, respectively) across 20 participants. A larger sample size is required to do further analyses on this. Further, there was no association between the different types of OST and severity of respiratory depression. Buprenorphine is thought to have a lower risk of respiratory depression and overdose rates compared to methadone and other OST medication, showing a ceiling effect (Dahan, 2006; Strang et al., 2017; Walsh, Preston, Stitzer, Cone, & Bigelow, 1994). Buprenorphine acts as a partial agonist, where even with full saturation at receptor sites, there is less than maximal effect compared to full agonists. Dose-response studies of buprenorphine have shown that there is a flattened or inverted U-shaped curve, demonstrating that at higher doses there is no greater or a decreased effect (Walsh, Preston, et al., 1994). However, there were no observed differences in the respiratory depression indices between users on methadone and buprenorphine in this study (Appendix: C-4 and C-6). Further discussion on this can be found later on in this chapter.

Overall, a greater frequency of respiratory depressant markers can be observed as a greater severity of respiratory depression. However, the question still remains – does this equate to risk of actual overdose?

5.8.6 Level of NRD in ODU with Lung Disease

There were no differences in drive between the two ODU groups but there were significant differences between the ODU group with lung disease and their corresponding controls. ODU participants with lung disease showed significantly lower levels of drive compared to their corresponding controls as well as in comparison to NRD levels reported in other studies of

COPD patients (Jolley et al., 2009; Murphy et al., 2011). In relation to this, however, the relationship between drive and measures of respiratory function and respiratory depression is uncertain. The levels of drive amongst ODU participants actually fell within the ranges seen in healthy adults (MacBean et al., 2016; Reilly et al., 2011), and were consistent with the previous study with a similar cohort (Jolley et al., 2015). A lower NRDI is evidently counterintuitive in the face of chronic use of opioids in combination with a higher likelihood of developing age-related diseases, including chronic respiratory disease where drive is required to increase to maintain adequate levels of blood gases. The data in this study therefore suggest that there is a chronic suppression of NRD by long-term opioid use, as demonstrated by a relatively inappropriately-low level of NRD relative to the severity of disease.

Aside from an expected trend towards a relationship between $ETCO_2$ and drive amongst the two control groups, no other respiratory marker or measure was correlated with drive in any of the groups. SpO_2% did not show any relationship with NRDI, however, this was not unexpected because pulse oximetry may not be as reliable an indicator of respiratory depression as other measures and is only a surrogate indicator of the effects of a drug on the ventilatory control system (Dahan et al., 2010; Jolley et al., 2015b). Even where baseline SpO_2% levels are normal, there can still be presence of opioid-induced reductions in NRD or increased $ETCO_2$% in line with opioid-induced hypoventilation (Jolley et al., 2015b) Additionally, several studies have reported hypercapnia in the presence of normal respiratory rates or oxygen saturation (Cronin et al., 2003; Dalchow et al., 2013; Herman et al., 1999; Jolley et al., 2015b; Kopka, Wallace, Reilly, & Binning, 2007) or reductions in respiratory rate but little change in SpO_2% or pCO_2 (Clemens & Klaschik, 2007; Pinna, Clemens, Quednau, & Klaschik, 2008).

The subsequent sections will further delve into the data to uncover key points that are of interest.

5.8.7 Further Examination of Results and Relevance to Key Mortality Issues

By focussing on the predominantly held mortality risk factors, it is possible to take a more in-depth examination into the results from this study. Of all the risk factors noted in this chapter as well as chapter 3, there are some factors which are thought to be well-evidenced and most influential on opioid-related mortality. The type of drug, age and route of administration are considered to be fundamentally important in vulnerability to overdose, and cigarette smoking to wider respiratory impairment issues. The rest of this section delves into some of the commonly-held statements by reflecting on the data described in this chapter.

Buprenorphine has less of a respiratory depressant effect than other opioids. It is a widely-held view that buprenorphine does not cause respiratory depression. Despite this, buprenorphine overdoses can occur, often due to the co-ingestion of benzodiazepines (Hakkinen, 2015; Megarbane, Hreiche, Pirnay, Marie, & Baud, 2006). Buprenorphine is referred to as a partial agonist and sometimes as a mixed agonist/antagonist, with the agonist or antagonist effect varying by dose, by receptor and between individuals (Jacob, Michaud, & Tremblay, 1979).

It is speculated that buprenorphine may be affected by other medication/drugs, particularly other depressants. The data in this study represented a good opportunity to find out whether there were any differences with people who were using buprenorphine with benzodiazepines or alcohol together. There were five ODU participants who used alcohol and were on buprenorphine and one person who used benzodiazepines as well as buprenorphine. Of the 12 ODUs who were on buprenorphine, there were no differences in the respiratory depression criteria between ODU who were co-using buprenorphine and alcohol compared to those who were not co-using other drugs. Only one ODU was co-using buprenorphine and benzodiazepines. There is clearly a limitation of sample size with this particular study, and it is difficult to make any conclusive statements in relation to the combined, or additive, effect of other depressant drugs. The limited data in this study suggest that buprenorphine may have a respiratory depressant effect, independent from other drugs. However, the case of buprenorphine is a seemingly more complex one. The two metabolites of buprenorphine are buprenorphine and norbuprenorphine, and a recent study (Strang et al., 2018) into its effects showed that the two metabolites may play opposing roles in respiratory depression, with buprenorphine appearing to antagonise the respiratory depressant effects of norbuprenorphine. This is also supported by animal studies (Ohtani, Kotaki, Nishitateno, Sawada, & Iga, 1997) but there is still very limited research into this.

Methadone deaths are more common in older age. There does appear to be an increased vulnerability amongst older users specifically with methadone (Gao et al., 2016; M. Pierce et al., 2018). However, as previously mentioned, it is still unclear whether this is a sensitivity to opioids or whether there is an issue of underlying chronic physical ill-health. It is possible to examine the data on age in further detail by splitting the data by median age into ‘younger’ or ‘older’ ODU. There were no differences between the two groups for any of the respiratory depression measures, except for basic lung function measure of FEV_1/FVC% ratio (Appendix: C-6). It is expected that the lung function measures would be related to age as COPD is a progressive disease that is more common in older aged people, and also, predicted lung function values incorporate age as part of the prediction calculation (Quanjer et al., 2012). However, it is interesting that there were no differences between younger and older age, suggesting that other factors are more important.

Injecting heroin is more likely to cause vulnerability to overdose than any other route of administration. According to reports, non-injection routes cause only 1% of heroin-related deaths (Darke & Ross, 2000). In terms of preferred and previous route of administration of heroin, there were no differences in the respiratory depression indicators between injectors (n=11), smokers (n=6) and both (n=3) (Appendix: C-6), except for $ETCO_2$ level which showed a significant difference between the groups. The highest average criteria were seen in the injectors group, with an average of 2.3 respiratory depression criteria. Of note, according to self-reports, whilst the majority of injecting drug users were only previously injecting heroin, a smaller proportion were still currently using (29%). In addition to this, as urine test results showed (see subsequent section), a greater proportion of ODU showed a presence of morphine/heroin in their urine analysis (55%), but it is difficult to state whether this was recent enough to impact the measures obtained on the study day or whether previous route of administration really does show a particular vulnerability. The specific issue of route of administration is covered in Chapter 6.

More severe cigarette smoking history means a greater vulnerability to respiratory system burden. Considering the high number of people who smoke and use drugs, and the increasing numbers of ageing heroin users, it is unsurprising that illnesses caused by smoking play a significant role in the causes of death and may also increase the susceptibility to opioid overdose (Jolley et al., 2015b; PHE, 2016b). Therefore, it is expected that the heavier the cigarette smoking history, the more likely the respiratory impairment. There were no differences in physiological responses amongst heavy, lighter and ex-smokers. The smoking pack history of the ex-smokers fell within the 'heavier' category, and thus, grouping the ex-smokers within the heavier smokers category again showed no differences between ex-smokers and current smokers in any of the respiratory function measures, encompassing the respiratory depression criteria, lung function measures and gas transfer (Appendix: C-6). This is relatively surprising, as one would expect that heavier smokers would show more severe respiratory impairment but the ability to draw definitive conclusions is again limited by the small sample size.

Staying in treatment for longer is more protective. There has been very little research into the association between length of time in heroin addiction treatment and risk of opioid overdose death. The available literature is centred on users being in or out of treatment and shows that being in treatment is generally protective (Cornish et al., 2010) against all cause mortality compared to no treatment at all but that the initial four-week period of treatment (Buster, van Brussel, & van den Brink, 2002; Caplehorn & Drummer, 1999; Degenhardt et al., 2009; DOH, 2017) and the immediate period after treatment ends are apparently vulnerable periods of time for users (Marina Davoli et al., 2007; Degenhardt et al., 2009). Based on cohort data, there is some evidence to suggest that mortality rates plateau after around the 50-week mark (Cornish et al., 2010). The question of whether the current duration of treatment has an actual acute effect on potential overdose risk has not been examined. From the data within this study, a median split of the data (12 months of duration being the median) showed no difference between shorter and longer duration of treatment amongst the respiratory depressant measures. Longer duration of treatment could suggest an increased stability on OST medication and opioid drug tolerance, however, the study did not thoroughly examine other factors that are associated with addiction treatment.

5.8.8 Veridicality

Veridicality is defined as 'the degree to which an experience, perception, or interpretation accurately represents reality'. The study measures incorporated questions on self-report additional drug and alcohol use, both on the study day and in more general. In addition, an alcohol breathalyser test and a urine test were used to examine presence of alcohol and seven drugs: Cocaine/Crack, Morphine (Heroin), Benzodiazepines, Methamphetamine, Cannabis, Methadone Amphetamine. A presence of morphine indicates use of morphine and/or heroin, usually within the last 2 to 3 days (Narongchai, Sribanditmonkol, Thampithug, Narongchai, & Chitivuthikarn, 2002; Standridge, Adams, & Zotos, 2010; Verstraete, 2004). In other words, if the only opioids taken are methadone and buprenorphine, it should not be present. Eight of the 20 ODUs had corresponding self-reports and urine analyses. Of the 18 subjects who were on buprenorphine or methadone, nine had a presence of morphine, indicating possible recent heroin use, and none of those declared any other drug use in the self-report question. Five ODUs had a presence of cocaine, and similarly did not report this. A presence of benzodiazepines, methamphetamine and/or amphetamine was detected in four ODUs where it was not self-reported.

There are clear advantages of using self-report over urine analysis, notwithstanding the practical aspect. However, it seems it is possible for this to be improved upon, and further, the methods incorporated in the self-reporting questioning in this study are not without problems. A truly blinded questionnaire would have been a more reliable measure of self-report and will be taken into consideration for future studies.

5.8.9 Additional Findings

Whilst not part of the original aims of the study, there were also some important unintended findings from the study. 65% of the opioid dependent users showed readings that indicated chronic obstructive respiratory disease, and only 38% of these had knowledge of this prior to the study. This is in line with previous studies and is important in the context of an ageing, drug user population who are increasingly prone to respiratory disease and risk of overdose (Jolley et al., 2015b; Palmer et al., 2012; Yadavilli et al., 2014). It has also previously been shown that respiratory diseases are prevalent amongst opioid users and in fact, can be considered more prevalent than matched controls (Jolley et al., 2015b; Palmer et al., 2012; Yadavilli et al., 2014).

5.8.10 How Does this Translate to Overdose Risk?

All measures examine respiratory depression differently. There is no gold standard of measuring respiratory depression, and the reasons for this are twofold: 1) that there are many potential mechanisms of respiratory depression (bradypnoea, reduced tidal volume as well as reduced responsiveness to hypercapnia caused by alveolar hypoventilation and hypoxaemia), and 2) technology and bioengineering is continually in development with regard to better and more reliable measures. It is for certain, however, that point measurements (one measurement of either SpO_2 or CO_2) are not sufficiently reliable to detect risk of respiratory depression (Dahan et al., 2010; Pattinson, 2008). The benefit of having all of these measures is the ability to extract the most suitable parameters for overdose detection. Using both end-tidal and transcutaneous capnography measures together simultaneously allows one to observe both the overall trends and breath-by-breath analyses. The benefit of measuring SpO_2 is its practical methodology as well as larger applicability in clinical and ambulatory settings. However, a change in SpO_2 is one of the final physiological effects that occur in respiratory depression. Oxygen saturation is a measure of gas exchange in the lung rather than a direct indicator of ventilatory efficiency (Dahan & Teppema, 2003; Dahan, van Dorp, Smith, & Yassen, 2008). In addition to this, SpO_2 is a peripheral measure of oxygen saturation and in clinical practice, it is a simple measure used to indicate a serious opioid-induced ventilatory event, together with 'looser' indicators of respiratory depression such as low breathing frequency and sedation (Dahan et al., 2010). Meanwhile, observed changes in NRDI is a measure of changes to the respiratory system prior to the occurrence of this said final result. Thus, NRDI is the most reliable of these to detect changes to the respiratory architecture.

There is a multifaceted and complex network of activity that underlies the components of an opioid overdose. An impairment in respiratory mechanics in comorbid lung disease impairs neuromechanical and neuroventilatory efficiency. Thus, the impact of respiratory depression by opioids is further compounded which may be relevant to overdose risk. Opioids cause a blunted responsiveness to ventilatory demand, hypercapnic ventilatory response, hypoxic ventilatory response, and, as I have shown, neural respiratory drive, which are the body's crucial signalling systems. Therefore, the greater the suppression of the neural drive to breathe, in combination with increased severity of lung disease, the greater the potential for respiratory depression, respiratory failure, and fatal overdose. This needs crucial further investigation. Studies examining this area have a difficult task because the reality of detecting whether indicators lead to fatal overdose is an obvious ethical obstacle and is very difficult to predict in live human studies. It is impossible to conclude with these data whether a summative effect is being observed, and this may well be an underlying factor.

5.8.11 Weaknesses of the Study

Age was not statistically matched and remained higher in the ODU-LD group when compared to the corresponding control group. One of the reasons for this was related to the fact that control samples were not specifically recruited for this study but had been selected from existing laboratory studies. However, one would expect that an older cohort would attain greater frequencies of respiratory depression due to the effect of the respiratory lung mechanics and lung function, but this does not appear to be the case. COPD is most commonly diagnosed in people over the age of 40, and crucially amongst those who smoke or are exposed to air pollutants and chemicals (BLF, 2016; Ramsey & Hobbs, 2006). Levels of oxygen saturation decrease in older age in healthy adults, and with a combination of COPD, it is not uncommon for levels to reach 88-92% saturation (Abdo & Heunks, 2012; BLF, 2016).

In relation to this, FEV_1%predicted values are based on age (as well as gender and height). The levels of FEV_1%predicted between the ODU-LD and controls-LD groups were not significantly differing, with some overlap between IQR (ODU-LD: 67-90%; Controls-LD: 53-75%). This suggests that the predicted values can actually account for differences in age between the two groups.

Further, as this was a convenience sample, the ratios between participants with and without lung disease, or between male and female participants, were not controlled for, which led to a smaller number of healthy ODU participants and also fewer female participants. Also, more generally, the sample size was too few to conduct more detailed statistical tests. Despite this, the data presented in this chapter were sufficient to fulfil the aims of the study.

5.8.12 Strengths of the Study

The findings of this study are important because there are currently no distinct data on the overlap between those with chronic respiratory disease, risk factors of overdose and measures of respiratory depression. There are obvious ethical considerations in studies such as these but this type of study methodology is practical and informative. It has shown that an investigation into chronic, everyday respiratory depression can be observed without disrupting the individual's treatment pattern or using pattern. Data presented in this chapter illustrate the ease of detection of respiratory depression and the need to explore the potential relationship with the suppression of NRDI and lung disease in ODU.

5.8.13 Possible Mechanisms and Implications for Clinicians

Using these types of intricate, detailed physiological measurements, we can identify markers that could be used to identify 'at-risk' patients. Reliable markers that are convenient, practical and immediate would be most useful for this but current techniques are not advanced enough for this to exist. SpO_2% is perhaps the most practical clinical measure but as demonstrated there are flaws in its clinical application (Dahan, 2006). It is feasible that these measurements could be conducted in patients before treatment and, in the future, even be used as a means of providing opioid users with better information on which to choose their treatment. These methods require validation in a larger scale, prospective study.

Further, more robust interventions need to exist in better identifying chronic respiratory diseases in this community. Even if overdose is not a potential risk/consequence, there is a clear requirement for this from the perspective of general health and well-being of this often multi-morbid population.

Most importantly, the greatest implication for clinicians and the wider public health domain is in the context of where these data can drive technology and allow for an early detection of risk of opioid overdose. The eventual aim would be to create a tool or a checklist to enable the understanding of opioid overdose liability, and for these tools to be implemented in a method that is fast-responding and life-saving. The next section will outline the future work that should be taken forward with these data.

5.8.14 Questions for Future Research

Deaths from opioid overdose could be prevented if the onset of the overdose could be detected. Informing future research into practical wearable versions of these measures in order to reliably monitor and ultimately prevent fatal overdose events is crucial.

Collaborating with other interested stakeholders and experts in bioengineering, mobile technology and physiology, these novel tools can be used to develop an experimental model of an acute, realistic overdose scenario. It would inform the development of devices that could detect overdose onset and trigger an emergency response. Future studies need to concentrate on taking this model further, i.e. how can we predict vulnerability to a fatal overdose? Determining physiological indices that are most suitable for mobile monitoring is the first step in this journey.

Summary

Conducting detailed physiological studies in a hard-to-reach population is a challenging task. However, being able to investigate such a group provides a great deal of detailed physiological information. Everyday respiratory depression exists within opioid-dependent users with and without lung disease. Compared to controls, there is a significant respiratory system 'burden' of lung disease. Being able to elicit these data by means of a simplified, practical method shows that it can be taken further into a clinical setting or inform further technological developments to better improve early detection of opioid overdose.

6 Exploration into the Effects of Differing Routes of Heroin Administration

6.1 Preface

Route of administration as a factor for opioid overdose has been addressed from many different perspectives. Whilst deaths can, and do, occur through non-injecting routes of administration of heroin (i.e. smoking, snorting and swallowing), the substantial majority of overdose deaths are still the result from injection of heroin (Darke & Hall, 2003). The understanding of the pharmacokinetic differences between different routes of administration are well-established and is the basis of much of pharmaceutical research and development. However, there is little understanding of whether, and why, the differing injecting routes of administration amongst heroin users actually relate to a higher risk of opioid overdose.

In the wider scope of my PhD studies, I had the opportunity to conduct secondary analyses on data that were collected by colleagues during a previous study which enabled me to examine the acute effects of injection heroin administration (these data were from an earlier study by my supervisors and colleagues (Jolley et al., 2015b). The data were not originally collated in order to examine the differences between routes of administration. The study aimed to investigate the acute respiratory depressant effects after a normal dose of diamorphine in patients who receive diamorphine as part of their maintenance treatment for their heroin addiction. However, as will be discussed in this chapter, the participants presented with a varied set of heroin use history and, therefore, the range of doses and routes presented in this chapter can be considered as reflective of the wider, long-term injecting heroin using population in the UK. Re-visiting this type of study was valuable in informing the future work described in chapter 8, which examined the impact of incremental dose changes.

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6.2 Introduction

Many long-term heroin users have peripheral veins that have been destroyed by repetitive injecting and consequent phlebitis, whereby the veins become inflamed. This is usually caused by blood clotting inside the vein or by damage to the vein walls. In this condition, users are usually left with finding alternative injecting routes of administration, such as intramuscular or subcutaneous, or non-injecting routes, such as intranasal or smoking (‘chasing’) (Girardin 2003). The pharmacological and subjective effects of intravenous and intramuscular routes differ in their absorption and initial onset. The different metabolites have different actions. It is known that the initial effects of heroin are attributed to 6-MAM and heroin effects after the initial drug effect are attributable to morphine. Intramuscular injection results in lower and delayed peak onset of the concentrations of the heroin metabolites 6-MAM and morphine (Girardin 2003). The peak effects of intramuscularly and intranasally administered heroin occur in 3 to 5 minutes (Skopp et al., 1997). Intravenous on the other hand, peaks in less than 1 minute.

Most fatal and non-fatal heroin overdose cases occur when heroin is administered intravenously. A case series on overdose fatalities in an emergency department in California, USA reported that the intramuscular route accounted for only 0.5% of non-fatal heroin overdoses (Sporer, 1999; Sporer, Firestone, & Isaacs, 1996). It is not clear whether this translates to a lower risk of overdose or whether there is just much lower prevalence of the use of intramuscularly administered heroin and subsequent overdoses. From the relatively limited literature that exists, there is a belief that the intramuscular route is a safer way to inject heroin. This route involves extensive peripheral hydrolysis and therefore, limits toxicity compared to that seen in intravenous administration (Way et al., 1960). Although it must be noted that any injection route carries risks, e.g. non-intravenous injection (particularly subcutaneous) may increase the risk of soft tissue damage (White, 1973).

Previous chapters have addressed the background of diamorphine maintenance treatment or heroin-assisted treatment (HAT). Safer heroin dosing in the patients who attend these clinics where dosing is supervised has been an integral part of the development of the clinics.

Generally, this is also applicable to advice and clinical recommendations to injecting heroin users in other types of clinics as well. Whilst encouragement to transition to less risky routes have been incorporated into clinical practice, to date, there has not been a clinical study that has compared the respiratory depressant and subjective effects from differing routes of administration of a single dose of pharmaceutical heroin.

In principle, the intramuscular route of administration should confer a lower risk of opioid overdose compared to intravenous administration which is more direct and has a more rapid and higher absorption of metabolites in the blood after injection. IV should also confer a higher subjective feeling of drug high because of the greater initial absorption and effect. Data in this chapter represent a secondary data analysis on a dataset from a study examining the acute respiratory depressant effects of a dose of injectable diamorphine. This chapter describes an exploration into the physiological and subjective effects between two common injecting routes of administration amongst long-term heroin users on diamorphine maintenance treatment.

6.3 Aims & Hypotheses

Aim 1: Is there any difference in physiological and subjective effects between an intravenous (IV) and intramuscular (IM) administration of heroin?

- Hypothesis 1: IV administration of heroin produces a more severe respiratory depressant effect and greater subjective experience of ‘drug high’ compared to IM administration.

Aim 2: Does IV administration produce more pronounced physiological and subjective effects in the initial first few minutes compared to IM administration?

- Hypothesis 2: IV administration produces more pronounced immediate and short-term (within the first minutes post-dose) physiological and subjective effects compared to IM administration.

6.4 Methods

6.4.1 Study Design

The sample of all analyses in this chapter was drawn from a previous study on acute heroin administration within a clinic that provided a stable maintenance dose of diamorphine. Any personal information pertaining to the participants had already been anonymised at recruitment stage of the study. The methods of this study were detailed in the 2015 publication by Jolley and colleagues (Jolley et al., 2015b). All participants were receiving injectable opioid treatment for heroin addiction within South London and Maudsley NHS Foundation Trust and had been on a stable dose for at least two weeks.

In total, 10 participants took part in the study and attempt was made to monitor all participants for 150 minutes post-dose administration. At 3 minutes prior to opioid drug administration, and then at 3, 8, 15, 30, 60, 105 and 150 minutes post-administration, participants were asked to rate their drug high, and their pupil size was recorded. All participants completed 30 minutes of recording after administration of their injectable heroin, and all underwent the following physiological measures:

- Parasternal intercostal muscle electromyogram recordings (EMG_{para}) providing an indication of the neural respiratory drive index (NRDI).
- Ventilation: respiratory rate, tidal volume and minute ventilation
- SpO_2% and $ETCO_2$%

6.4.2 Indicators of Significant Respiratory Depression

The following respiratory-related indices were used in the study as evidence for significant respiratory depression:

- Absence of inspiratory airflow for more than 10 seconds
- $SpO_2 < 90\%$ for more than 10 seconds
- $ETCO_2$ % per breath exceeding 6.5%

Participants were stimulated if apnoea persisted for longer than 15 seconds.

6.4.3 Subjective Drug Effect

Participants rated their drug high on a scale of 0 (no effect) to 5 (maximal effect). The staff rating of intoxication was measured on the same scale of 0 (no effect) to 5 (maximal effect). Staff level of consciousness was assessed using rating scale of 1: normal; 2: visibly affected but alert; 3: drowsy but responds to verbal stimuli; 4: no response to verbal stimuli.

6.4.4 Statistical Analysis

The participants were divided into those that had administered their heroin dose intramuscularly and those that administered intravenously. Non-parametric bivariate testing was used to assess the differences between the participants. Examination of within-subject differences used Friedman's Test to test for differences between baseline and successive time points for both groups (IV and IM). Kruskal-Wallis test was used to identify differences between groups at each time point and Mann Whitney U Test (U-statistic) was used to test for differences between groups at specific time points. Data analyses were performed using GraphPad Prism 7 for Mac OS X (GraphPad Software, Inc) or SPSS software v22 for Mac (SPSS Inc, Chicago, Illinois, USA). Significance was determined at values of $p < 0.05$ level or at $p < 0.01$.

6.5 Results

6.5.1 Demographics

The median (and interquartile range) age of the participants was 49 years (42 to 58 years) (Table 6-1). Three of the participants took their diamorphine took via intravenous route and seven took their dose via intramuscular. Doses ranged between 50mg to 100mg for intravenous, and 90mg to 200mg for intramuscular. Nine of the 10 participants had COPD as measured by spirometric and clinic criteria.

Table 6-1: Table of demographics and basic opiate prescription information, Median (IQR). BMI: Body Mass Index.

Age (years)	**Sex (M/F)**	**Height (m)**	**BMI (kg/m^2)**	**Prescribed Opiate**	**Does (mg)**	**Route of diamorphine**
49 (42-58)	8M/2F	1.8 (1.6 -1.81)	21.6 (19.3-25.3)	All injectable diamorphine plus oral Opiates: 7 Methadone, 2 Oral morphine	100 (75-160)	3 IV 7 IM

6.5.2 Physiological and Objectives Measures of Respiratory Depression

6.5.2.1 Pulse Oximetry

The median (IQR) SpO_2% amongst participants in the IV group was 95.3% (92% to 95.7%). The IM group had a median (IQR) SpO_2% of 96.4% (94.8% to 98%). Neither IV nor IM groups showed significant changes from baseline to successive time points post-dose (Q=7.5, p=0.1 and Q=7, p=0.1, respectively). There was no statistically-significant difference between the two groups across the 30-minute recording as well as within the initial first few minutes post-administration (H-score=12.5, p=0.19).

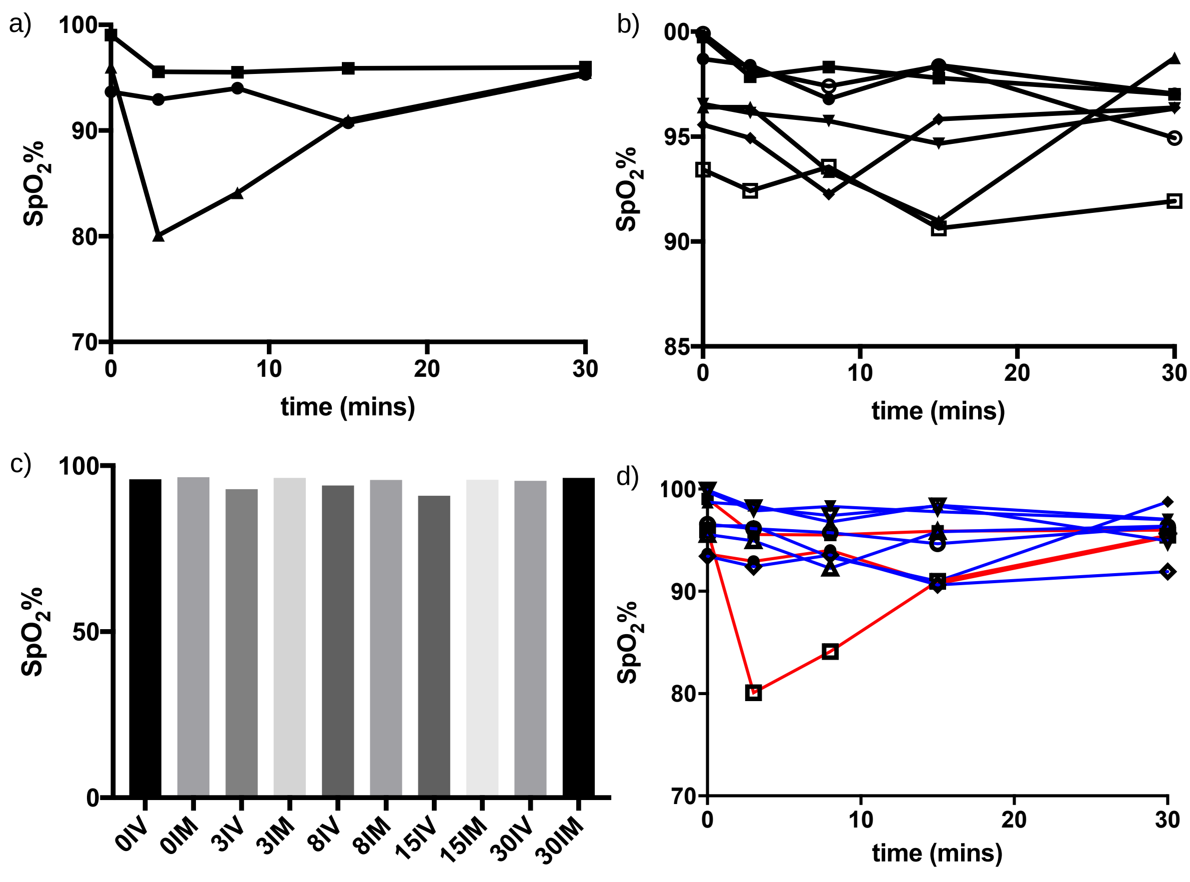

Figure 6-1a-d: Results for pulse oximetry (SpO_2%) over time.
a) three IV participants; b) seven IM participants; c) bar graph of the differences between IV and IM administration at each time point: 0, 3, 8, 15, and 30 minutes post-dose; d) all participants, IM (blue) and IV (red).

6.5.2.2 End-tidal carbon dioxide

The median (IQR) $ETCO_2$% was 4.65% (4.4% to 5.2%) in the IV group, and 5.4% (4.8% to 5.9%) in the IM group. A significant change from baseline to successive time points post-dose was seen in the IM group (Q=11, p= 0.03), but not in the IV group (Q=6.7, p=0.2). In the initial first few time points post-dose, $ETCO_2$% was higher in the IM group compared to the IV group, but this was not significant (H-score=13.9, p=0.13). Overall there was no statistically significant difference between the two groups.

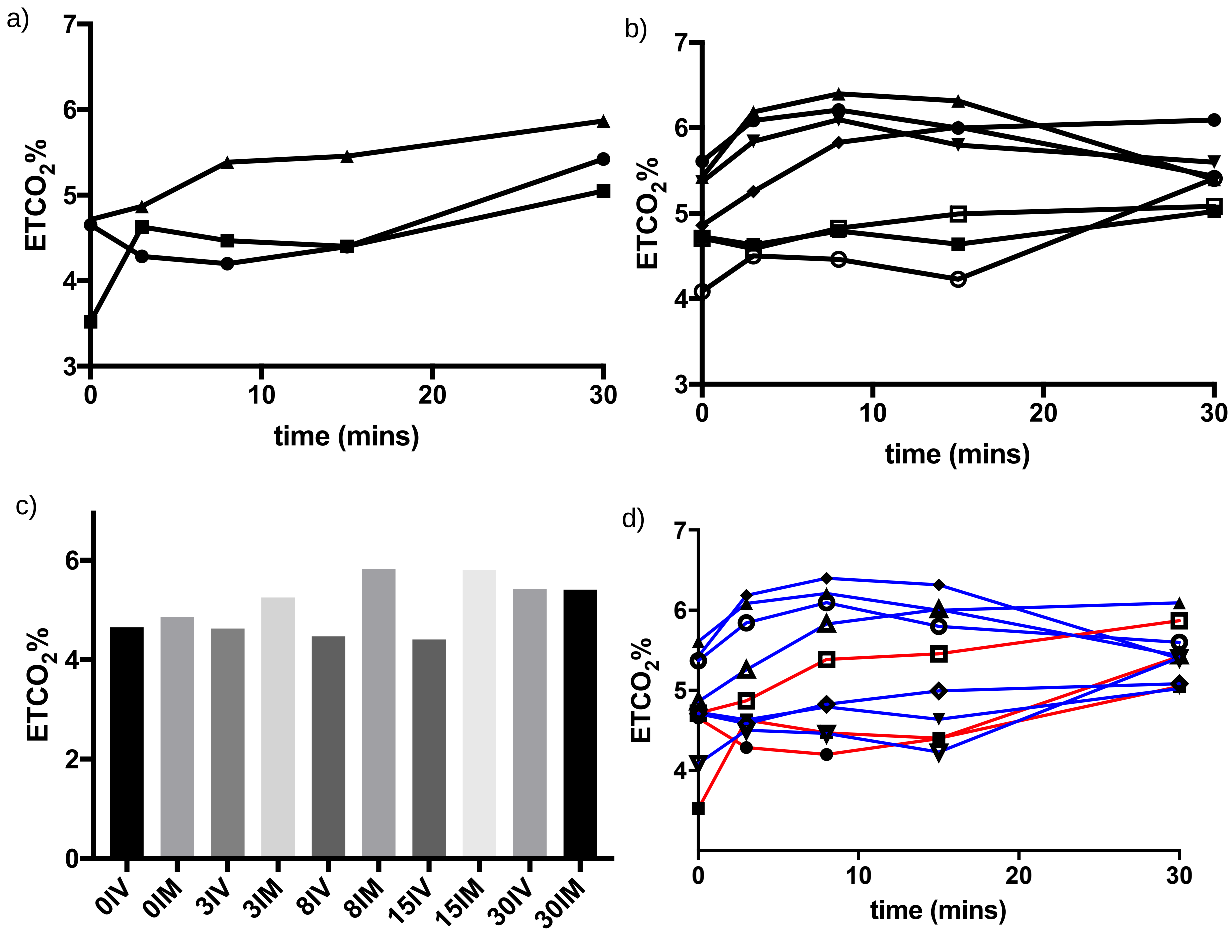

Figure 6-2a-d: Results for end-tidal carbon dioxide ($ETCO_2$%) over time.
a) three IV participants; b) seven IM participants; c) bar graphs of the differences between IV and IM administration at each time point: 0, 3, 8, 15, and 30 minutes post-dose and d) all participants, IM (blue); IV (red).

6.5.2.3 Respiratory Rate

The median (IQR) respiratory rate was 8.95 breaths/minute (7.85-9.63breaths/min) in the IV group, and 10.27 breaths/minute (8.92-13.25breaths/min) in the IM group. Neither IV or IM group showed significant change from baseline to successive time points (Q=0.5, p=0.9 and Q=6,p=0.2). Generally, the respiratory rate was higher in the IM group compared to the IV group at each time point, but this was not significant. Overall there was no statistically-significant difference between the two groups (H-score= 8.5, p=0.5).

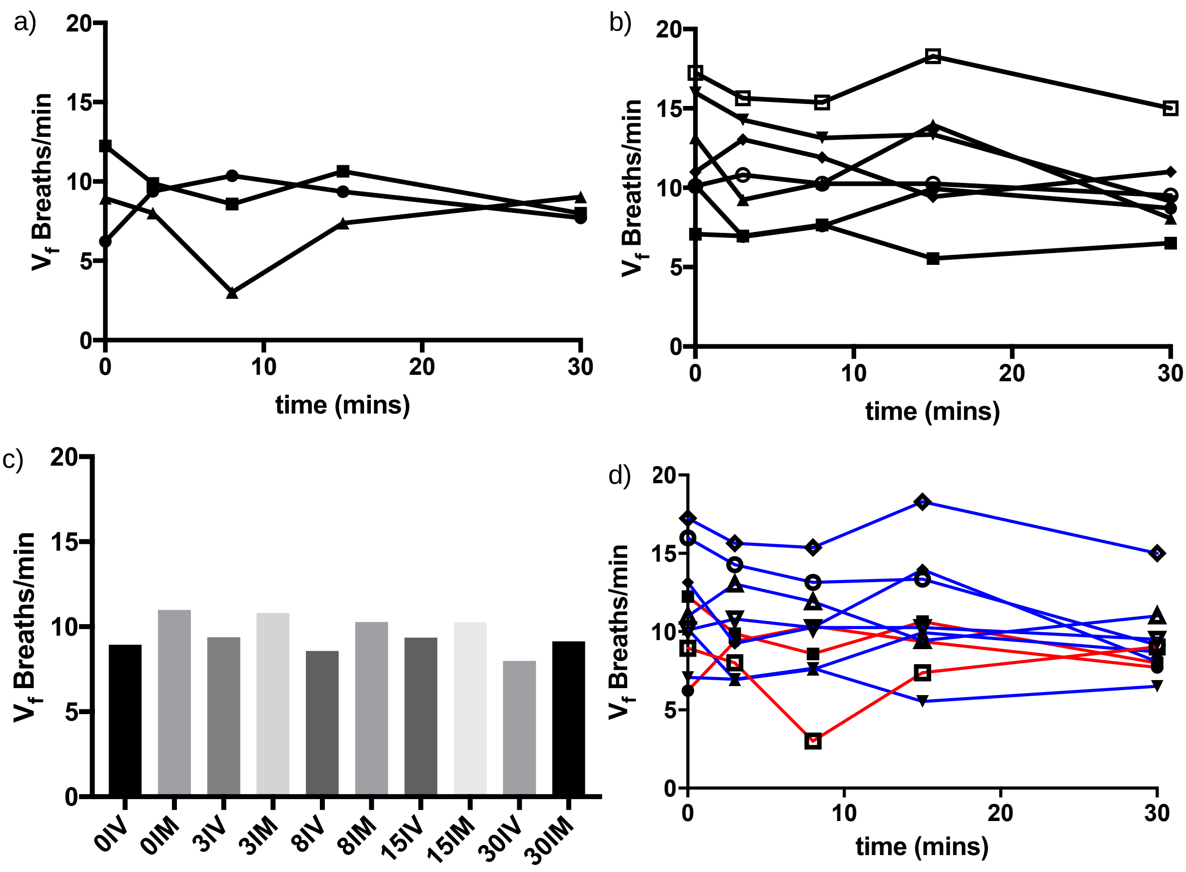

Figure 6-3a-d: Results for respiratory rate over time:
a) three IV participants; b) seven IM participants; c) bar graphs of the differences between IV and IM administration at each time point: 0, 3, 8, 15, and 30 minutes post-dose and d) all participants, IM (blue); IV (red).

6.5.2.4 Neural Respiratory Drive Index (NRDI)

The median (IQR) NRDI was 68.73 min^{-1} (56.77-161.99min^{-1}) in the IV group, and 107.33 min^{-1} (76.14-129.22 min^{-1}) in the IM group (with a median of 75.4min^{-1} and 120min^{-1} at baseline, respectively). There were no differences from baseline to successive time points post-dose for either IV or IM groups (Q=3, p=0.6 and Q=7,p=0.4). Overall, NRDI was higher in the IM group compared to the IV group at each time point, but this was not significant. Overall there was no significant difference between the two groups (H-score= 4.4, p=0.9).

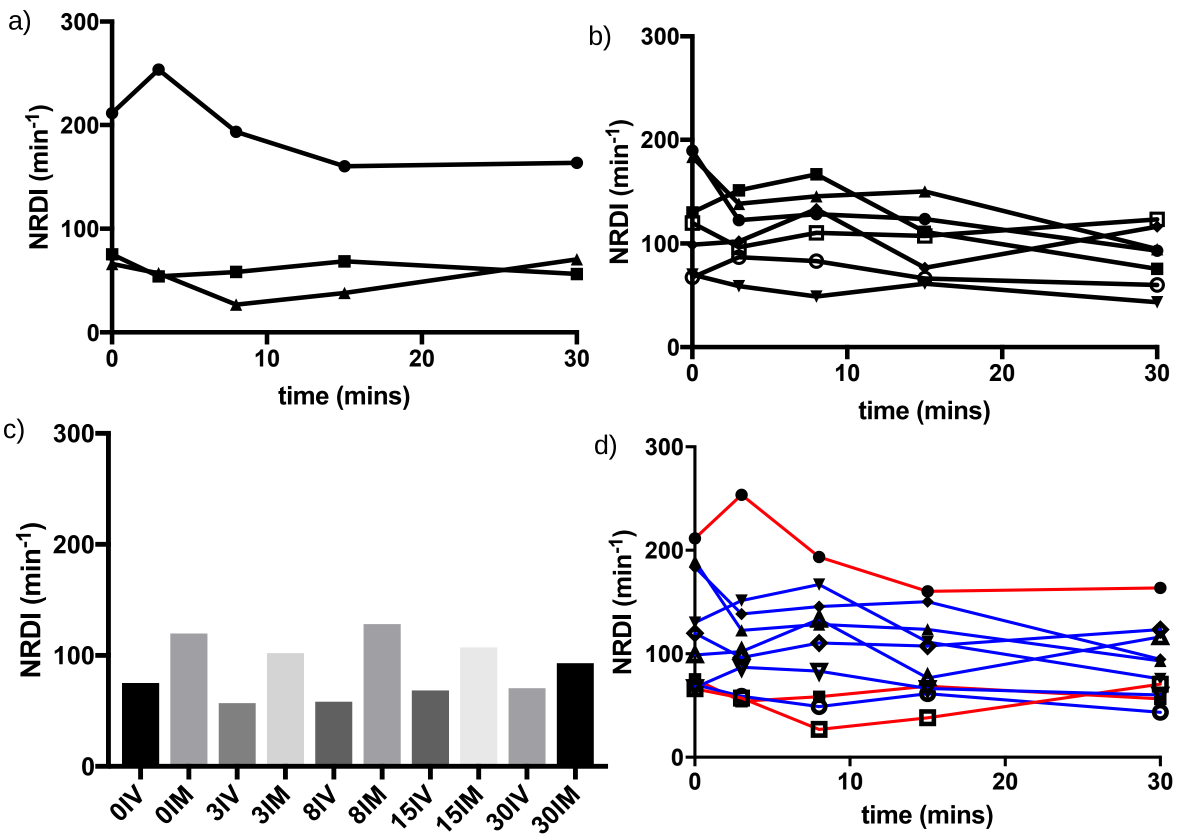

Figure 6-4a-d: Results for EMG_{para}%index (NRDI) over time:
a) three IV participants; b) seven IM participants; c) bar graphs of the differences between IV and IM administration at each time point: 0, 3, 8, 15, and 30 minutes post-dose and d) all participants, IM (blue); IV (red).

6.5.2.5 Tidal Volume (VT)

The median (IQR) VT was 1.02L (0.78-1.42L) in the IV group, and 0.92L/min (0.71-1.01L) in the IM group. There were no differences from baseline to successive time points post-dose for either IV or IM (Q=6, p=0.3 and Q=3,p=0.5). There were no statistically-significant differences between the two groups with regard to tidal volume (H-score=6.6, p=0.7).

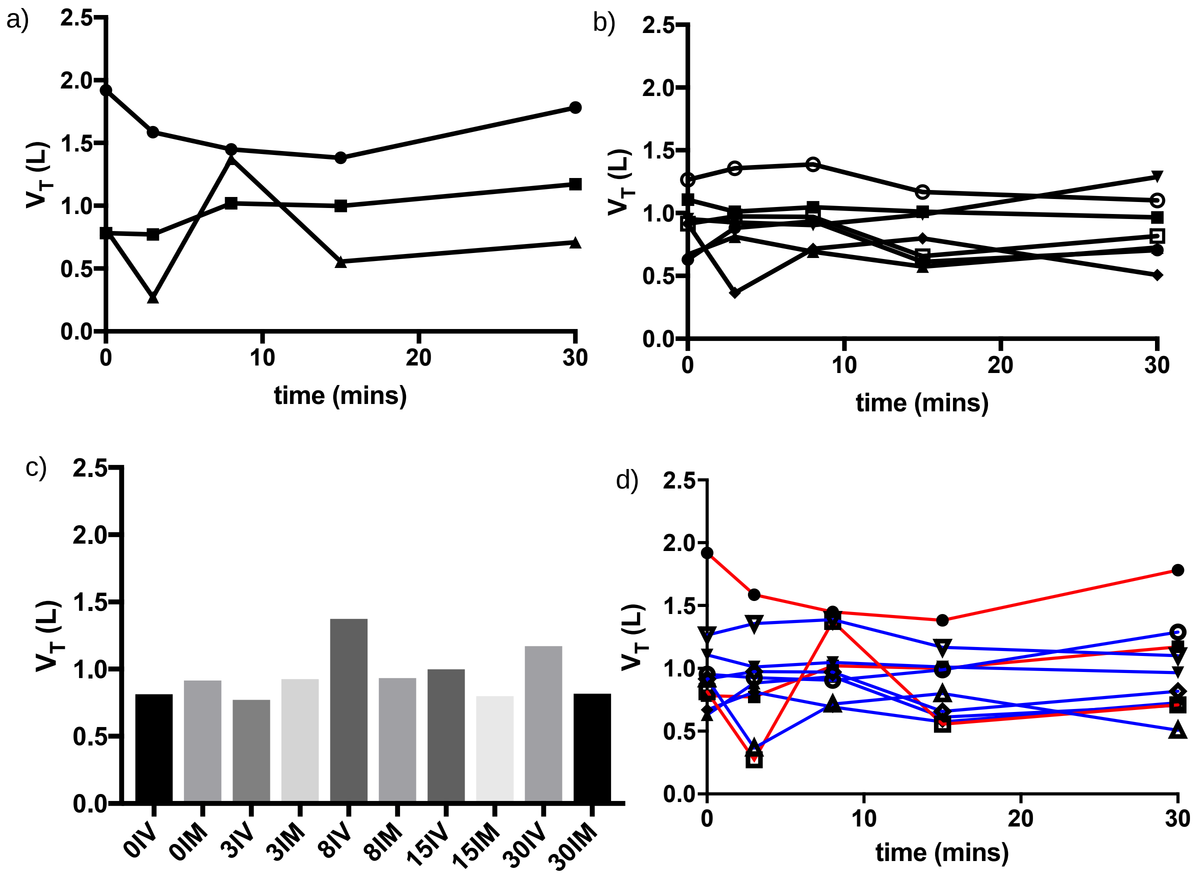

Figure 6-5a-d: Results for tidal volume (VT) over time:
a) three IV participants; b): seven IM participants; c) bar graphs of the differences between IV and IM administration at each time point: 0, 3, 8, 15, and 30 minutes post-dose and d) all participants, IM (blue); IV (red).

6.5.2.6 Minute Ventilation (V_E)

The median (IQR) V_E was 9.35L/min (6.84-12.44L/min) in the IV group, and 8.52L/min (6.71-12.53L/min) in the IM group. There was a significant change from baseline to successive time points in the IM group post-dose (Q=13, p=0.01), but not the IV group (Q=2,p=0.8). Overall, there were no significant differences between minute ventilation amongst the two groups. There did appear to be a higher minute ventilation in the intravenous group at 15 and 30 minutes post-opioid dose administration but this was not significant (H-score= 3.5, p=0.9).

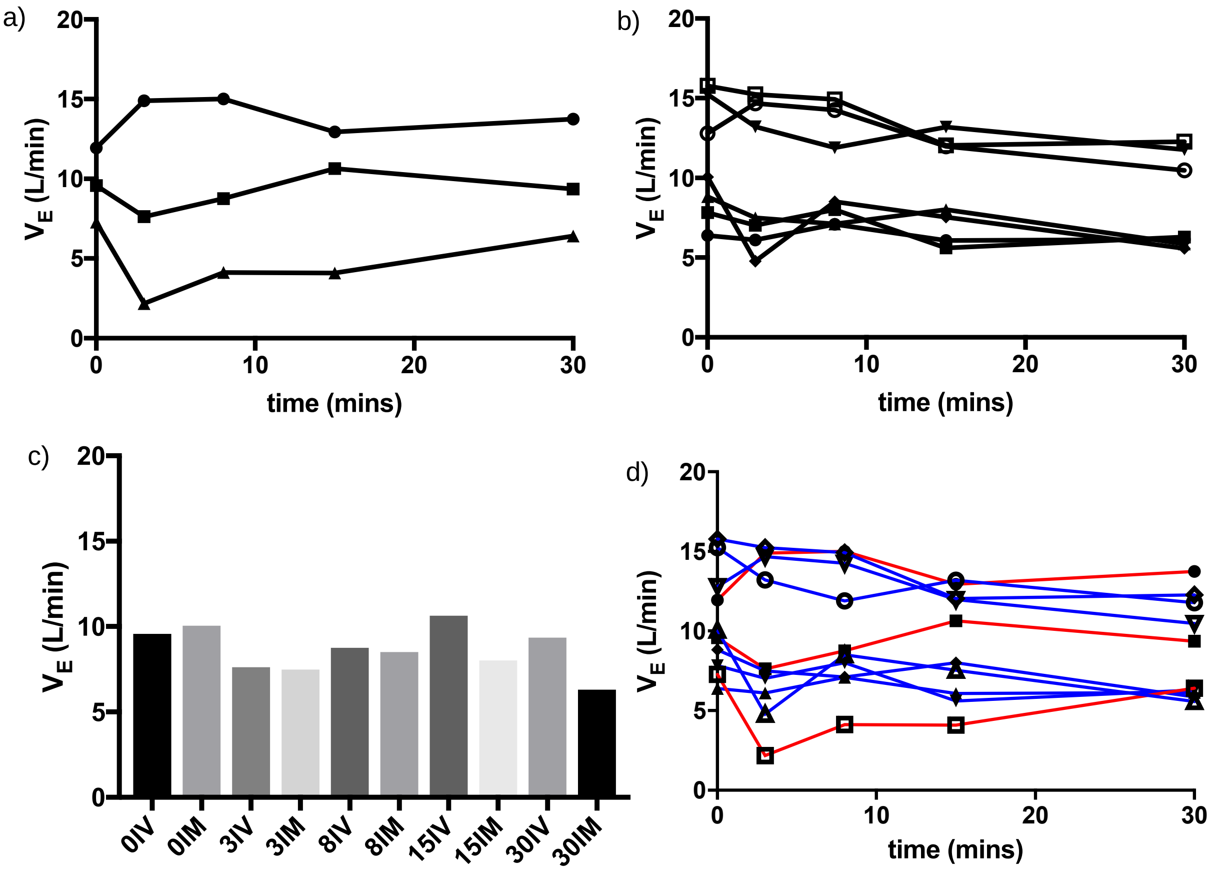

Figure 6-6a-d: Results for minute ventilation (V_E) over time:
a) three IV participants; b) seven IM participants; c) bar graphs of the differences between IV and IM administration at each time point: 0, 3, 8, 15, and 30 minutes post-dose and d) all participants, IM (blue); IV (red).

6.5.2.7 Pupil Size

The median (IQR) pupil size was 2mm (2-2.75mm) in the intravenous group, and 3mm (3-4mm) in the intramuscular group (3.5mm and 4mm, respectively, at baseline). The IV group did not show any difference from baseline to successive time points (Q=8, p=0.07) whereas the IM group showed significant difference at 8 minutes post-dose (Q=14.9, p=0.02). However, the IV group showed significantly more constricted (smaller size) pupils at the 3-minute post-dose time point compared to IM group (Figure 6-7c; U-statistic= 1.5, p=0.033).

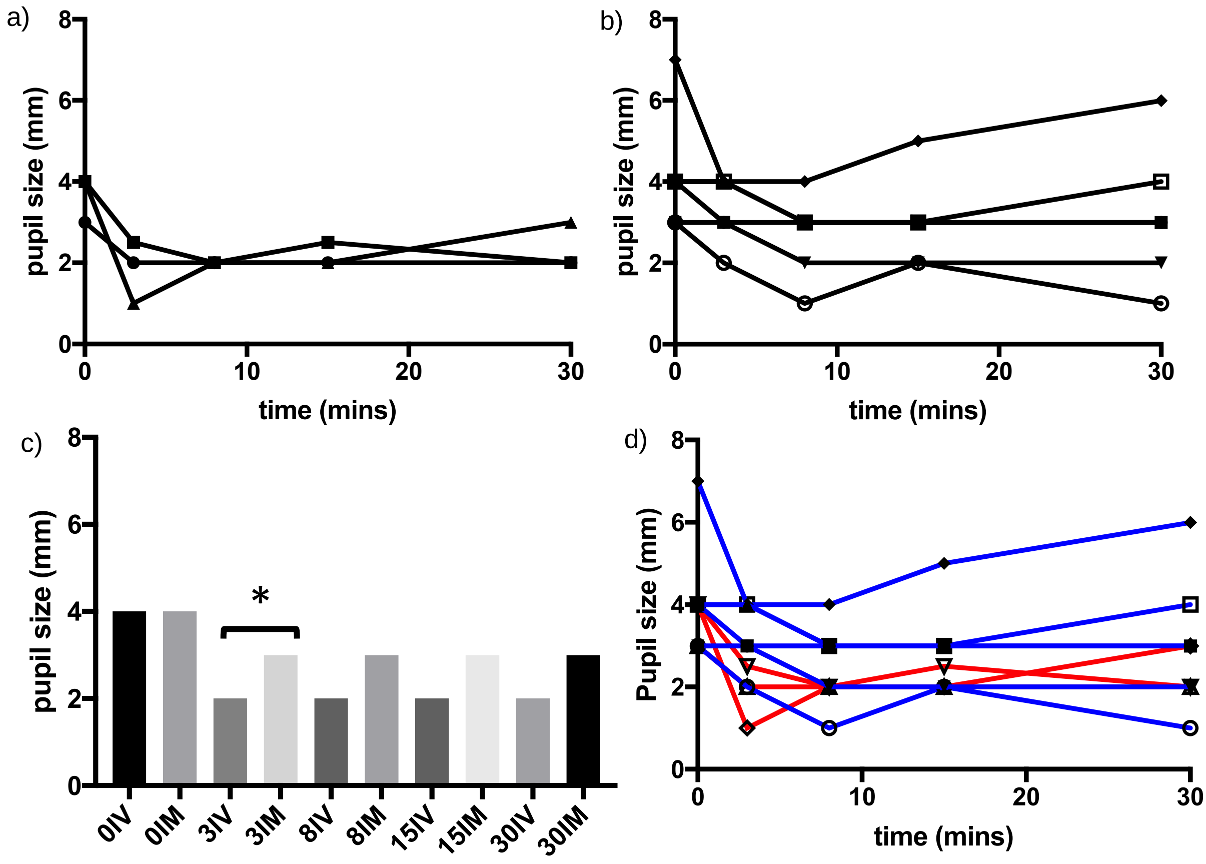

Figure 6-7a-d: Results for pupil size over time:
a) three IV participants; b) seven IM participants; c) bar graphs of the differences between IV and IM administration at each time point: 0, 3, 8, 15, and 30 minutes post-dose and d) all participants, IM (blue); IV (red).

6.5.3 Subjective Measures of Drug Effect

6.5.3.1 Level of Consciousness

The median (IQR) Level of Consciousness (out of 4) was 1 (1 to 1.5) in the IV group, and 1 in the IM group. Neither the IV or IM group showed a significant change from baseline to successive time points (Q=4, p=0.9 and Q=8, p=0.1). Overall there was no significant difference between the two groups across any time point (H-score: 6.1, p=0.7).

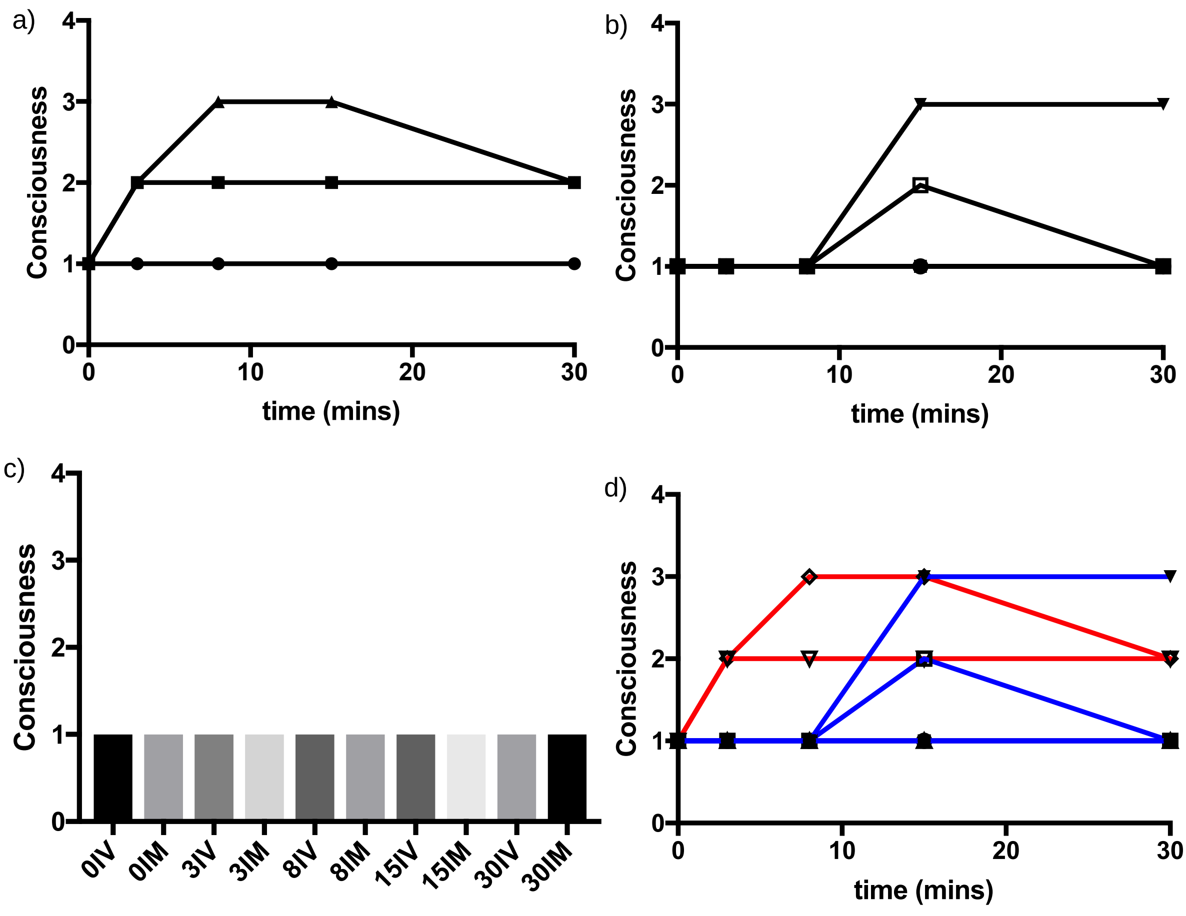

Figure 6-8a-d: Results for level of consciousness over time:
a) three IV participants; b) seven IM participants; c) bar graphs of the differences between IV and IM administration at each time point: 0, 3, 8, 15, and 30 minutes post-dose and d) all participants, IM (blue); IV (red).

6.5.3.2 Subjective High

In the IV group, the median (IQR) of the subjective rating of drug high was 2 (1.5-2.25) out of the maximal effect of 5. In the IM group, participants rated their high at 2 (1-2) out of 5. Both IV and IM groups showed significant differences from baseline to successive time points post-dose (Q=11,p-0.002 and Q=25,p=0.0001, respectively). At the 3-minute post-dose time point, the IV group showed a significantly higher rating of drug high compared to the IM group (U-statistic=0, p=0.017). Other time points did not show any difference in subjective high.

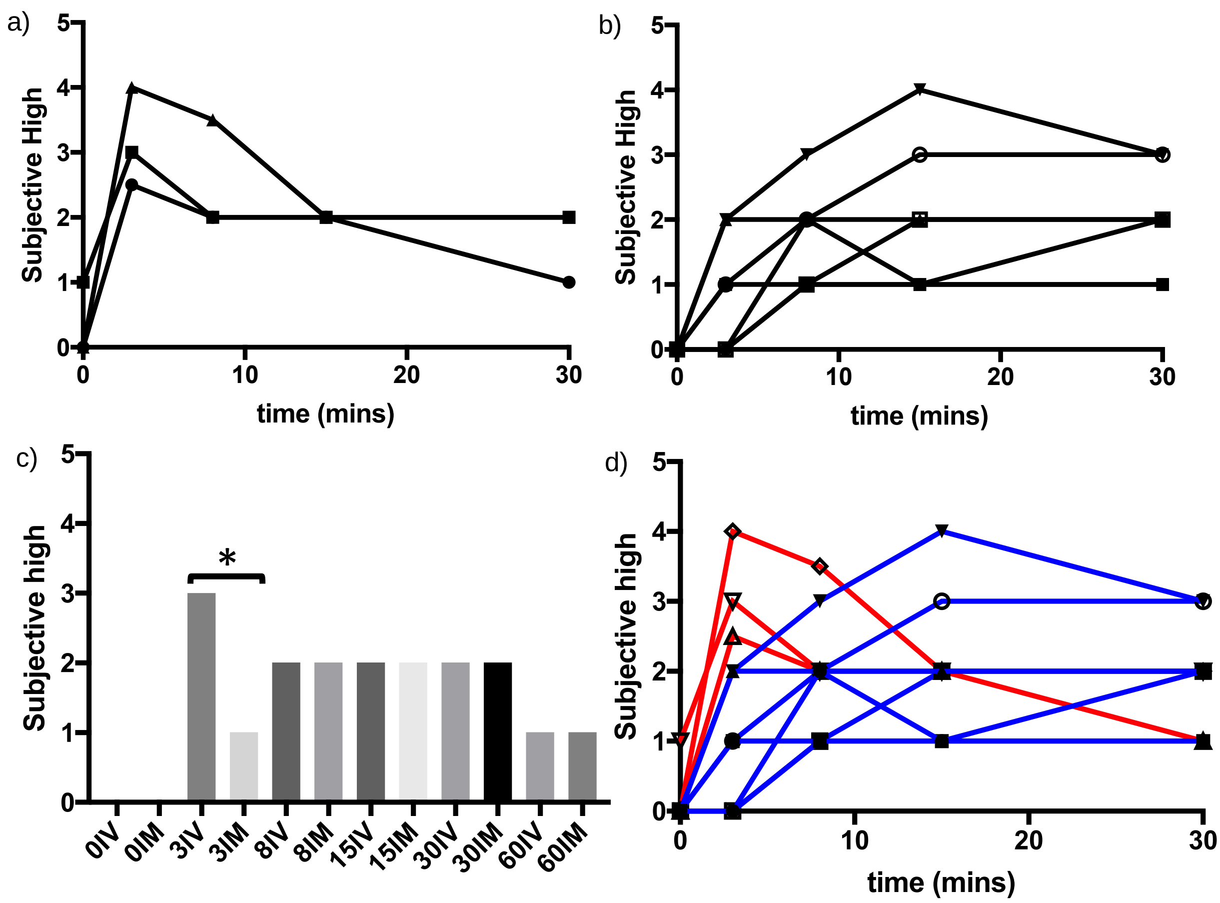

Figure 6-9a-d: Results for subjective high over time:
a) three IV participants; b) seven IM participants; c) bar graphs of the differences between IV and IM administration at each time point: 0, 3, 8, 15, and 30 minutes post-dose and d) all participants, IM (blue); IV (red).

6.5.3.3 Staff Rating of Intoxication

The median (IQR) rating of intoxication (out of 5) was 1 (0 - 3) in the IV group, and 1 (0 to 2.5) in the IM group. Neither group showed a significant change from baseline (Q=5, p=0.3 and Q=8, p=0.1). At 3 minutes post-dose, the IV group showed a higher level of intoxication compared to the IM group, but this was not significant. Overall there was no significant difference between the two groups (H-score= 13, p=0.2).

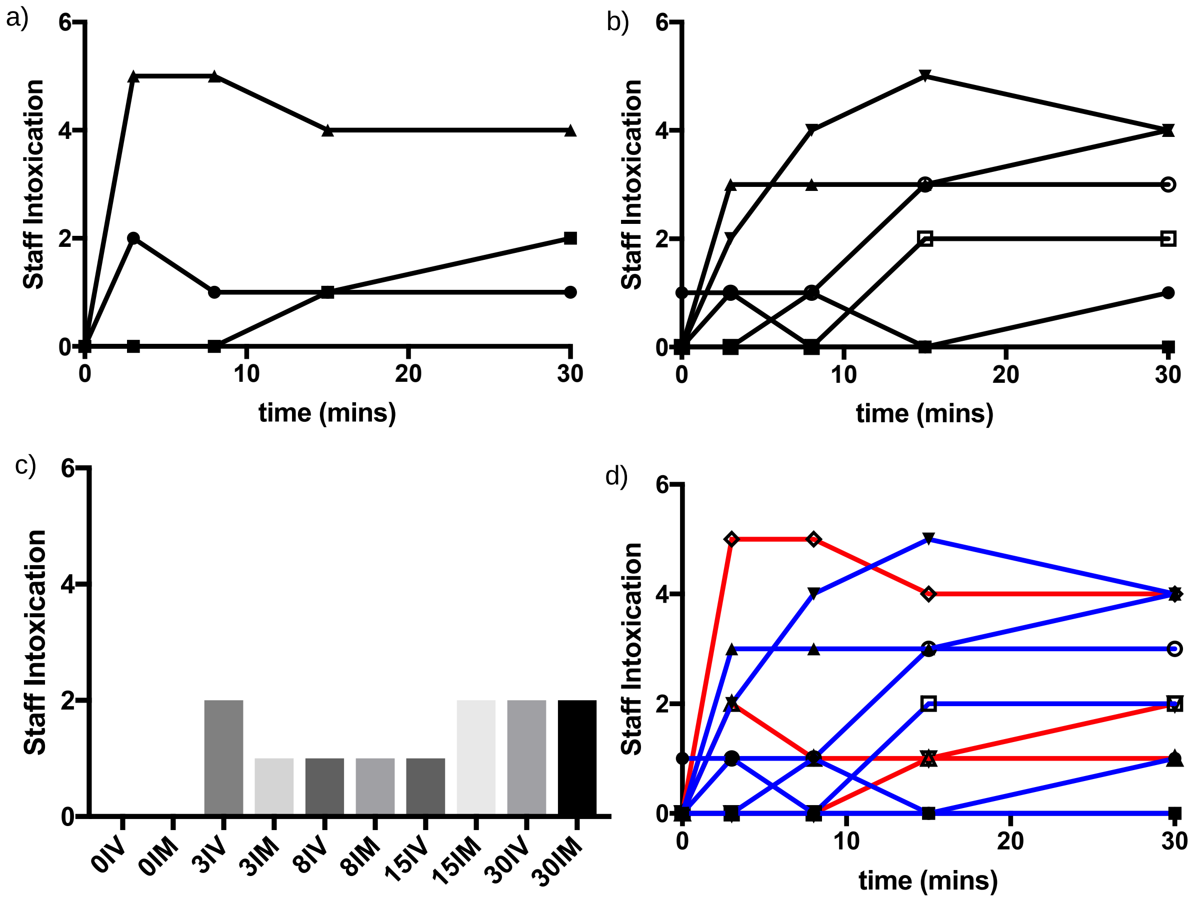

Figure 6-10-d: Results for staff intoxication over time:
a) three IV participants; b) seven IM participants; c) bar graphs of the differences between IV and IM administration at each time point: 0, 3, 8, 15, and 30 minutes post-dose and d) all participants, IM (blue); IV (red).

6.5.4 Indicators of Respiratory Depression

One participant was found to have all of the indicators of respiratory depression, which was previously reported (Jolley et al., 2015b). This participant had administered IV and this dose was the highest IV dose amongst the IV group (100mg). The other IV participants did not show any of the indicators of respiratory depression; their doses were 50mg and 60mg.

Amongst the IM group, there were two participants who administered the same 100mg as the IV participant stated previously, however, only one of the IM participants showed one of the indicators of respiratory depression (respiratory pause for longer than 10 seconds). Out of the other five IM participants, three experienced two indicators of respiratory depression, and two experienced one indicator.

6.5.5 Changes from Baseline

Similar diverse observations were noted for physiological changes from baseline. In the IV group, the relative % change from baseline to nadir was 1.1% to 4.3%. The IM group showed decreases in SpO_2% from baseline of between 0.6% to 4.6%. The % change from baseline to peak $ETCO_2$ also varied between the groups. The IV group saw a range of between 5.1% and 39.1% relative change from baseline to peak $ETCO_2$%, whereas the IM group saw a range of 0.01% to 34% change. Respiratory rate saw a diverse range, from 7% to 48.8% and 4.9% to 37% between the IV and IM group, respectively. EMG_{para}%index (NRDI) ranged between -26.6% to 17.9% from baseline to nadir in the IV group, and 9.9% to -54.5% in the IM group.

6.6 Discussion

6.6.1 Summary of Results

Results from the data presented in this chapter are of a varied physiological and subjective response to differing routes of heroin administration. The only statistically-significant difference between the IV and IM administration groups was in subjective effect and reduction in pupil size which were significantly more pronounced in the IV group compared to IM in the initial 3 minutes post-dose.

6.6.2 Implications and Limitations of this Chapter

The physiological responses that occurred in this study were an expected part of the opioid effect. However, the expected difference between IV and IM were not apparent in the data presented in this chapter. The reason for this is most likely due to the fact that the number of participants in each group are not sufficient to draw detailed conclusions on the data. However, age did not vary greatly in this group, and chronic lung disease was present in all except one participant. Additionally, these types of studies are notoriously difficult to recruit for, given the limited size of the population, but have a high level of within-subject design which provides in-depth physiological data for each participant.

Pupil size showed a significant difference between the groups. Pupillary light reflex is a commonly used evaluation in medicine generally to detect injury to the central nervous system such as stroke, traumatic brain injury, etc. Opioids induce miosis (excessive constriction of the pupils) by causing contraction of the circular muscles that consequently constrict the pupil response to light (Ellis, 1981; Fountas et al., 2006). It is well-understood that the signs of an opioid overdose involve pinpoint pupils, i.e. pupils that are very small in diameter, and pupillometry is a validated and recognised diagnostic criterion of overdoses (Friedman & Manini, 2016; Larson, 2008; Stead, Stead, & Kaufman, 2006). This is usually combined with decreased level of consciousness and respiratory depression. Pupil size did appear to show a significant difference at the 3-minute post-dose time point between the IV and IM group which is consistent with previous literature (Rollins, Feiner, Lee, Shah, & Larson, 2014). This finding warrants further and more detailed research to examine whether this relationship is consistent in a larger sample size.

It is also interesting that pupillary responses were the only objective measure that showed any difference between the two injecting routes of administration and ventilatory responses were not. This may be due to the individual subject factors that influence ventilatory parameters and are difficult to control (e.g. talking, level of agitation, etc.), whereas pupillometry is a measure observed in a truly objective manner. It could also be related to the fact that pupil diameter is regulated by different regions within the brainstem compared to respiratory control. Opioid-induced pupillary effects are caused by disinhibition of the pupilloconstrictor nucleus in the pretectal region of the brainstem (Larson, 2008). Other studies have noted the importance of using pupillometry over other measures as a marker of pain thresholds in anesthesia as it is shown to be more sensitive to noxious stimulation (Constant et al., 2006; Larson et al., 1993; Paulus et al., 2013) and in an experimental model of opioid antagonism developed in Norway (Skulberg et al., 2018).

Finally, this study was a comparison between IM and IV. Whilst IM does occur, the more common non-IV route is smoking or ‘chasing’. Unfortunately, the participants recruited in this study were only on an injectable form of diamorphine and therefore, the study design was limited to these routes. An inhalable form of diamorphine does exist and is used in heroin-assisted treatment clinics in the Netherlands (Blanken, Hendriks, Van Ree, & Van Den Brink, 2010; Brink et al., 2003) but is not available in the UK. In the future, it would be relevant and important to also compare IV with chasing, and possibly even intranasal administration of heroin (which carries greater risk of overdose but is much less common) perhaps among an illicit heroin-using population.

6.6.3 Additional Findings

It is important to highlight that the participant who administered the highest IV dose (100mg of diamorphine) also showed the most significant impairment in the study. The oxygen saturation recording for this participant reached a low level of 73.6%. Considering the dips in SpO_2% for other participants did not surpass levels below 85.6%, this is a remarkably distinct response. The levels of other physiological responses also showed similar pronounced effect such as NRDI which was $26 min^{-1}$ at nadir, when the median for the group as a whole was $109.5 min^{-1}$, as well as respiratory rate which dipped to 3 breaths/minute at the 8-minute time point.

An interesting point to note with this particular participant was that, as well as experiencing the most significant physiological changes post-dose, they also experienced the highest effect of drug high. This was not unexpected but it is interesting as these particular participants are long-term injecting heroin users who have been using diamorphine for, in most cases, many decades. In the case of this participant, the number of years of injecting drug use exceeded 40 years. Despite this length of time injecting heroin, the drug effect is still pronounced. This drives the question of whether other subjective effects were also experienced, such as drug liking. This is an important issue in discussions about addiction treatment more widely and is beyond the scope of this thesis.

In relation to the prolonged nature of the respiratory depressant effects, it is interesting that all participants showed sustained markers of respiratory depression throughout the monitoring period. There were two individuals who showed abnormally low levels of SpO_2% before the dose was administered (below 95%, participants 1 and 10) and a further three participants showed abnormally low respiratory rates (below 10breaths/minute, participants 1, 4 and 7). None of other participants or measures showed abnormal levels pre-dose. However, those with abnormal pre-dose levels appeared to show the same levels of physiological markers post-dose as the other participants (Figures 6-1 to 6-10), i.e. they were not 'more extreme', and the pre-dose irregularity did not appear to cause more of an impact on their response to the IV and IM heroin dose.

6.6.4 Wider Implications of Exploring Non-intravenous Routes of Administration

Injecting routes of administration are highly reinforcing because of the initial rapid onset and greater bioavailability. Intramuscular is less intense than intravenous and may be less risky; this prompts the question, should users be encouraged to switch to intramuscular (Strang et al., 1999; Swift, Maher, & Sunjic, 1999)? Previous literature has discussed the potential benefits of encouraging users to switch to non-injecting routes in order to reduce the related harms and risk of overdose (Darke & Hall, 2003; Hunt, Griffiths, Southwell, Stilwell, & Strang, 1999). Literature on the practical application of the switching of routes within a clinical setting is limited. The Randomised Injectable Opioid Treatment Trial (RIOTT) protocol considered this in relation to implementing clinical practice of encouraging a move to IM. Clients within this trial were generally all IV users. However, as part of their trial, when IV administration was unsuccessful, it was established that the procedure would be addressed as follows: after three unsuccessful attempts at superficial vein injecting, and if no blood was in the syringe, the clients were asked to inject IM or subcutaneously (SC). If this was refused, or if a significant amount of blood is seen in the barrel of the syringe, then IM or SC would be not given, and an oral dose was issued instead. It was also stated that clients who repeatedly have difficulties injecting IV would be reviewed by their key worker or medical officer. This encouragement to change route of administration was not necessarily based on reducing risk of overdose but it is useful to reflect on the dynamics that this transition may represent for users in these types of settings. Indeed, this issue is one that concerns clinicians in the addictions field more widely. There is anecdotal information of clinicians encouraging IM use over IV, but evidence for how commonly this occurs or how effective this is still unknown. This further highlights the importance of exploring this area in future research.

6.6.5 Questions for Future Research

Heroin users clearly administer heroin intravenously for a reason. It gives users a greater rush, and higher peak effects. The data presented in this chapter show the need for further research into two areas: firstly, further analysis into the physiological and subjective differences between the two common injecting routes, and secondly, the qualitative aspect of why individuals chose to use heroin IM or IV.

An important way forward from these data would be to expand this type of exploratory physiological and psychological study and examine whether variation of dose effect exists between IV and IM within the same subjects. In a controlled setting, this could be a strong way of ensuring that the dose effect is in fact related to the route itself. The other question for future research is in the understanding of the experiences of users within the context of how and why differing routes of administration are chosen.

The question remains whether people choose to IM simply because of limited/restricted venous access or whether there is a more nuanced aspect to this that should be explored. In a similar vein, it could be compared to choosing between a stronger %ABV such as whiskey, over a weaker %ABV such as beer on certain days, or in certain circumstances over others. Should we do qualitative analysis into why people who have chosen to IM and why they would actually prefer IM if they had the physical capacity to IV?

Conclusion

Intravenous administration of heroin is the route most commonly observed in cases of fatal and non-fatal opioid overdose. Previous literature suggests that intramuscular administration may be less toxic and potentially safer option of injecting heroin. Data presented in this chapter cannot definitively support the hypothesis that IV heroin administration produces more pronounced respiratory depressant effects compared to IM heroin administration. However, the data represent valuable preliminary information for future studies and introduces further questions for exploration. Further, more detailed analysis into individual cases showed that the highest IV dose also produced the highest respiratory depressant response. These experimental studies are difficult and ethically challenging. Therefore, opportunities to examine previously conducted data must be pursued. It is important to develop these questions further in order to be able to determine safer alternatives that can be implemented into clinical practice.

7 Clinical Trial and Error

7.1 Preface

This chapter is focussed on describing and highlighting the preparatory work that was involved in setting up the clinical trial on acute opioid overdose or ‘AOO’. It is important to highlight the preparatory work as these particular types of experimental studies within academic settings are few and far between, probably for many good reasons. I start the chapter by describing the development of the study protocol which involved establishing a set of questions, guided by the qualitative Reader Dr Jo Neale. I consulted a number of former and current service users with these questions and held several discussions with experienced clinicians and academics in order to refine and develop the study design and protocol. It was crucial that we prepared the protocol in this way as it is important to enable this study design to be not only robust, but also, to be used as a model for future research studies.

The latter part of this chapter delves into the administrative, procedural and, even at times, political obstacles that became part of the journey of this study. These steps took the better part of three years to undertake and have given me an incredible insight into real-world research that would not have been possible otherwise. It also, hopefully, strongly demonstrates the challenge involved in developing and conducting this type of research in practice.

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7.2 Development of AOO Study Protocol

Development of the study protocol involved a number of processes. This section will highlight the consultation process with former and current service users. The initial consideration was regarding the dose of the opioid, and how we determined the increase of 10% and 20% of normal maintenance dose. Other important considerations were of the randomisation and blinding processes, respiratory depression indices and the cut-off levels for use as the study parameters; the latter of which had to be established without jeopardising the safety of the patient or quality of the study.

7.2.1 Dose Increases

Several reputable studies that have conducted this type of increased opiate dose have successfully shown that an experimental study can be implemented without any serious side effects to the subjects. A Dutch group conducted a double-blind randomised study to address the pharmacological differences between inhalation and intravenous routes of heroin administration, taking patients from the Heroin on Medical Prescription Research Project in the Netherlands. Their regular doses alternated between 67%, 100% and 150% (Rook et al., 2006). Other studies have looked at high dose effects of opiate substitution drugs, such as methadone or buprenorphine. Curran and associates focused on the craving effects of a 33% increase in oral methadone to patients who are on a daily dose of methadone (Curran et al., 1999).

From a risk assessment perspective, these were seen as increases with minimal harm. In this study, the proposed +10% and +20% of regular dose of diamorphine was expected to show significant changes but with minimal harm to the subjects and their treatment plans. Subjects were recruited from clinics where they were already receiving a dose of diamorphine. Patients in these clinics normally self-administered their dose separately throughout the day. This study only impacted one part of the patient’s dose.

7.2.2 Randomisation and Blinding

In the original concept of the study, a study design resembling the 2x2 crossover design (Lintzeris et al., 2007, 2006) was to be implemented. This was when the study design included the element of co-use of diazepam. The design was based on a series of studies that had examined the pharmacodynamic effects of co-administering high dose methadone or buprenorphine with high dose diazepam. Participants in these studies were recruited from the Randomised Injectable Opiate Treatment Trial (RIOTT) clinic and a comparison of the effects of 100% and 150% of the maintenance dose, as well as 0mg and 40mg of diazepam, using physiological measures and Visual Analogue Scales were made (Lintzeris et al., 2007, 2006). The design for the AOO study was originally to include a placebo control for diazepam along with the diamorphine doses and thus, incorporated this 2x2 design. It was not deemed appropriate to include a placebo for diamorphine as the treatment regimen is such that it would potentially cause the user to destabilise, which was not the aim of the study. The protocol and study design were eventually revised and co-administration of diazepam was excluded from the study. While this research question is still crucial to investigate, it was thought that a focus on diamorphine would strengthen adherence rates and quality of the study and, as a result, this was prioritised. Other reasons that also influenced this exclusion are explored further on in this chapter.

There were also plans to include double blinding, whereby only the trial pharmacist would be aware of the diamorphine dose levels and the sequence of randomisation. However, the cost of randomisation, but more significantly, the de-randomisation process were seen as obstacles for this to be implemented. The de-randomisation process is such that there could potentially be a delay in relaying the actual dose used in the session, and thus, in an emergency situation, it was deemed inappropriate to incorporate a full randomisation and double blinding strategy. In addition, the Ethics Committee and other specialists specifically enquired about the procedures in place for a potential situation in which a participant experiences a serious adverse event in one of the sessions, and whether they would be re-invited for further sessions. We decided that a dose escalation was the most appropriate way to manage this. It is clearly unusual for a clinical trial of a product that has been around for over a century to incorporate features that are more commonly associated with a Phase I study. However, it was still important to incorporate a form of randomisation and blinding for the purposes of study reliability. It was, therefore, decided that a single blind, single randomisation strategy would be established. The participants were told that a dose increase of 10% and 20% would be implemented, but that they would not know when these would be given, and the order, according to the participants, was randomised. Initially, it was conceived that the blinding would be implemented via over-labelled or masked syringes. However, this procedure was quoted at a prohibitively high cost. The final decision to add water per volume that was the same for each participant, according to their dose, was implemented in the final protocol. Ultimately, the study relied on relative flexibility to the study design to reflect the realistic using scenarios that it aimed to capture, and to guarantee the safety of the participants. As a result, some of the methods, while scientifically sound, were not usual. The quality and objectives of the study were maintained throughout all of the novel practical implementations.

7.2.3 Consultation with Other Researchers and Clinical Specialists

Discussions were also held with various clinical colleagues (Dr James Bell, Dr Ian Winston and Mr Rob van der Waal) working in the clinical team associated with RIOTT in order to ascertain over the degree to which an increase to a patient's diamorphine dose is suitable, as well as the cut-off limits of the safety measures. Discussion of the safety measures, as well as respiratory depression indices, were held across multidisciplinary groups, with the advice of members of a respiratory medicine research group. Specialists in this group included critical care consultants, respiratory medicine consultants and other allied experts, alongside academic supervisors and co-investigators.

7.3 Consultation with Service Users

Service users were consulted about the feasibility and acceptability of this study. At the time of the consultation, the plan was to include study sessions with co-administration of benzodiazepines, e.g. diazepam. However, for reasons stated earlier and to be stated in the latter part of this chapter, this particular section of the study did not go ahead as originally planned. It is an area that is expected to be explored in continuation of this study after the PhD, and therefore, is still included in the discussion of the protocol.

Voluntary service users from the target population were recruited through a UK-based drug charity for consultation. The consultation took the form of one-to-one interviews, and Dr Jo Neale, a qualitative Reader in Addictions, provided the necessary guidance over the structure of these interviews. The aim of the consultation was to gather information on whether the study design was suitable and feasible, and to address the potential concerns of administering an increase to a maintenance dose. The consultation informed the methodology of the study protocol. The consultations were initiated with a brief description of the study. The description was verbally iterated along the following lines:

> The study is aiming to look at what happens in an overdose. It aims to address the myth that high dose heroin and, separately, that co-administration of benzodiazepines, are likely to increase the risk of overdose. We haven't yet tested these things in a proper scientific setting but they are received wisdom in the medical field.
>
> A consultation of this type is to gather information about what is considered most acceptable and reasonable. It is open for you to comment and make any suggestions you think would be necessary.
>
> Some information about the study that we know so far:
>
> - Each study session will last a maximum of three hours.
> - People who are on diamorphine treatment will be asked to participate.
> - Two main questions will be answered: 1) is high dose heroin more likely to cause overdose; and 2) is co-use of benzos more likely to cause overdose?
> - In each session, each participant will take one placebo or active diazepam tablet AND diamorphine IV, either their normal or an increased dose.
> - Payment and travel reimbursements will be issued.

Questions were asked in five separate sections, each addressing different components of the study design; 'Increased Dose of Heroin', 'Co-use of Valium', 'Future Studies', 'Study

Conditions' and 'Recruitment'. The questions and summarised responses for each section have been described as follows.

7.3.1 Increased Dose of Heroin

1. Do you think it is reasonable to ask people to increase their dose by 10% for the purposes of this study?
2. Do you think it is reasonable to ask people to increase their dose by 20% for the purposes of this study?
3. Do you think it is reasonable to ask people to increase their dose by 50% for the purposes of this study?
4. If there is an increase, is it acceptable to have a decrease? By 10%? 20%? How far do you think it could go either way?

None of the service users stated that a 10% or 20% dose increase would be an issue, or that people would be reluctant to participate because of this dose increase. One user said that 20% or 25% would be 'much of a muchness'; and also, '50% would probably show some difference with intravenous, but perhaps not intramuscular users'. They all stated it would depend on the actual dose they are receiving. Finally, an increasing stepwise approach to the opioid dose was suggested by all users.

7.3.2 Co-use of Valium (diazepam) or other sedatives

1. People who are already using benzodiazepines will be excluded from the study because it will not be safe and will skew the results. However, what do you think about asking people who have had a history of benzo use? E.g. haven't used for 30 days. Do you think it is reasonable?
2. Initial thoughts are to have a low dose of Valium (10mg) with the normal heroin dose. The daily recommended is 30mg. Do you think this is reasonable?
3. What would be their reaction if a higher dose (20 or 30mg) of Valium was requested?
4. What about adding an inactive benzodiazepine dose (placebo)?

None of the service users thought that it was unreasonable to include individuals who were on diazepam as well as diamorphine, and that it would be sensible to start at a low dose first before increasing. One user suggested including people who were using Temazepam as well. Ultimately, this aspect of the study was not continued any further, with the focus being maintained on diamorphine, and the aim to include co-administration of other depressants at a subsequent stage after the study.

7.3.3 Future Studies

1. Alcohol and heroin? Again, we will have to exclude people already drinking heavily, do you think this is reasonable?
2. What about heroin at normal dose and alcohol at varying doses or vice-versa?

All the services users said that alcohol would more likely be the root of these problems in much the same way that benzodiazepines are. One stated that 'alcohol seems to go hand in hand with heroin, especially with people who don't know where or when their dose is coming from. Alcohol is definitely more commonly used'.

7.3.4 Study Conditions

1. Timing: do you think three hours is an unacceptable period of time?
2. Would you be ok with taking your drugs in a laboratory setting?
3. Would you be ok being wired up at the same time?

The timing and study setting were not considered as unacceptable and it was thought that these particular participants would be used to taking their doses in clinical settings.

7.3.5 Recruitment

1. Do you think £60 supermarket vouchers are suitable payment/remuneration?
2. What If I ask 20 people, how many do you think will agree? Why/Why not?
3. What will be their biggest concern and what would be their reaction?
4. What is the best way and best time to approach people?

When asked how much was to be given, all said that £60 would be insufficient. At the time of consultation, there were three sessions proposed, in the final version of the protocol, the number of sessions was increased as it was important to examine the effect of new settings, and particularly of new clinical settings. This meant that the amount of money given was also increased to £100 to reflect this. The method of providing an escalating scale of vouchers was used, and this was based on the research conducted by colleagues at the National Addiction Centre through its work on contingency management (Weaver et al., 2014). One of the larger scale studies examined the potential significance of providing financial incentives for Hepatitis B vaccinations amongst drug users in drug treatment and showed that adherence improved significantly. These findings around reinforcement and the emergence of the idea of a reinforcing 'completion bonus' informed the protocol and escalating voucher provision for each of the visits incorporated in this study.

7.3.6 Summary of Service User Consultations

Overall, one of the biggest challenges that was raised, and one which had a direct impact on the implementation of the study, was the issue of blood sampling. All of the consulted service users stated that people's biggest concern and problem would be fear and paranoia about blood tests. It was noted that many of the potential participants approached for the study would be chronic injecting drug users, and whose venous access had been an issue in other settings, such as routine blood tests or liver function tests. The AOO study protocol did not include blood testing, and instead required participants to have had a liver function test prior to participation in the study. Most of the areas covered by the consultation were met positively by the service users and the consultation process was invaluable to establish the most appropriate strategies in the study.

7.4 Clinical Trial Process

The clinical trial process, from initial conception to invitation of first participant, has been an arduous and complicated journey. Many aspects of this journey have seemed completely unexpected and, at times, even unbelievable. This particular study is without a doubt a challenging one, and for many people who interacted and assisted along the process it was unfamiliar territory. It would not be possible to cover all aspects of this process in this thesis. This section of the chapter reflects on some of the specific themes and obstacles that were observed within this unfamiliar situation. These reflect the interpersonal interactions, the challenging and hard-to-reach population and the often-difficult requests put upon the variety of people who were involved in the process. A timeline of events can be found in Appendix D.

7.4.1 The Type of Study You Have Will Define the Next Three Years of Your Life

The initial process of the study required the definition of the type of study, which caused much confusion. As it was a study examining a particular treatment but maintaining the same medication that patients had been using, it was unclear whether it would be classified as a standard clinical study or a clinical trial on a medication, officially termed Clinical Trial of an Investigative Medicinal Product (CTIMP). However, it was not a study on the treatment *per se*, but on the dose of the medication. These types of studies are most common in Phase I clinical trials, which are minimally available for diamorphine/heroin effect.

In January 2015, an application as a non-CTIMP clinical study was initiated. This was initially questioned within the local Risk Assessment Committee (RAC), which assesses studies' pre-ethics applications. A RAC predominantly ensures that a study is generally acceptable and financially viable. In order to assess whether the study was a CTIMP or not, a summary of study was sent to the Medicine and Health Regulatory Authority (MHRA), which uses an algorithm to determine whether a study is a CTIMP. In the end, after several months of being referred from one organisation to another, the study was deemed a CTIMP.

7.4.2 Never-Ending Liaisons with the Clinical Trials Office

As soon as a study is determined as a CTIMP, a Clinical Research Associate (CRA) is connected to a study. Usually, one CRA is assigned to each study prior to the relevant application processes and immediately prior to the ‘kick-off’ meeting. A kick-off meeting involves all relevant parties (funders, research, facilities and administrative staff) to meet and assign the required activities to relevant people; in reality, it took four months to set up this meeting due to the sheer number of attendees. Furthermore, a CRA assists with anchoring the study and the study documents to the legal and procedural requirements of all CTIMPs which are governed by national and European Union legislation. This particular study, in the end, involved two different CRAs, and a further three who covered or supervised the main CRA. However, CRAs generally do not work in one office, but instead, are based from home, and travel across the country on monitoring visits (CTIMPs require regular monitoring to ensure that all aspects of the study are in place). As a result, many of the discussions with CRAs were via email and some via telephone. This has, in many ways, been helpful to retrace many of the concerns, issues and obstacles that were raised throughout the study. The number of email exchanges reached quantities that has been impossible to quantify. The importance of having face-to-face meetings, however, has its own advantages in establishing a good connection and understanding between you and the CRA, and is important in the context of navigating the complex maze of conducting CTIMPs. Fortunately, in the later stages of the study, this was actually experienced with the final CRA that we were assigned.

7.4.3 Unexpected Outcomes and Discussions with the Ethics Committee

The main ethics meeting was conducted on 12th October 2016 and both my supervisor, Professor Sir John Strang and I attended this meeting. It was fully expected that questions on safety and participant recruitment would be a priority. The greatest concerns, however, appeared to be related to the justification of payment in vouchers and further clarifying the fatal risks in the participant information sheet. For example they stated:

> After the researchers had left the meeting, the Committee raised a concern regarding the £100 voucher that participants would receive. Although the voucher would be awarded in staged payments, the Committee requested written justification for this as they could be sold for cash .This could provide incentive to some participants to partake for that reason alone.

The particular issue of voucher payments is discussed in some more detail in the previous section. Moreover, in the meeting itself, we also met some unexpected questions from the Committee. One of the Committee members, a Clinical Pharmacologist, began his query as a very specific question about the scientific value of the study. He stated that the purity of street heroin had an enormous variability of strength, and that, because we would only be impacting a small dose range of diamorphine, he asked how we would be replicating the street doses without introducing too much risk. However, most interestingly, he asked whether we should just continue with the dose escalation until we felt uncomfortable. We responded by stating that we had also discussed this dilemma and we were aiming to maintain the correct balance. We stated that once we had explored the more 'comfortable' territory of a 10% and 20% increase, that we would consider investigating a higher dose increase of, for example, 40% in separate future studies.

7.4.4 Your Clinical Research Associate Explains Your Study Better than You Can

Once the CRA is assigned, the intricacies of the CTIMP world become ever more complicated. There are two site initiation visits, one for pharmacy staff, and another for the study site staff, which both involve meeting all relevant staff involved and introducing the protocol and the procedures to the relevant parties. While this is clearly a useful element of the process, the reality of conducting these types of meetings without a specific Trial Manager or Research Coordinator (I acted both roles) was a challenge. However, the establishment of good relationships with the CRA proved important. In one of these meetings, our CRA showed a keen interest in diamorphine prescribing: during her talk about her role and the regulations that, in reality, most of the staff had heard in one form or another on many occasions, she also incorporated a description about the study, and a very detailed overview about diamorphine prescribing, which surprised and impressed me. CRAs do not need to be informed about the details of the background of the study being implemented, but it was positive to hear the relaying of information about a form of treatment that is often overlooked.

7.4.5 No More Heroin Anymore

After initial ethics approval, there is an opportunity to reach out to recruitment sites and establish connections. This process was slightly complicated in this study. When the Randomised Injectable Opiate Treatment Trial (RIOTT) was officially closed down in 2015, due to the cessation of central government funding and a lack of local funding, there was immediate concern as to how the study would proceed. It was known that there would be a period of time in which the patients of RIOTT would slowly be re-integrated back into standard drug treatment and/or that their treatment would continue within standard drug treatment centres. It was always expected that there would be a sufficient pool of patients to draw from. However, when contact was made with relevant services in various regions of London and the South East of England, it became clear that the pool to recruit from had reduced and that it would be insufficient to recruit the required numbers. Fortunately, many of the services in these and other areas of the UK agreed to be included in the study. The first substantial amendment incorporated the addition of these services as 'PIC' sites (Participant Identification Centres).

7.4.6 Top Deals and First-class Delivery

With regard to the ordering and delivery of diamorphine and other drugs, there were some interesting discrepancies in the manner in which they were proposed. Diamorphine ordering was not an issue, and we did not observe any obstacles in the process, neither financial nor procedural. In fact, when the time came to order the diamorphine, the particular size of ampoules were 'on contract' and essentially were on offer (*100mg x 5 vials = £18 plus VAT, The 100mg vials are usually £42.39 but are on contract at the moment).* Not only was this the cheapest aspect of the study, the delivery of diamorphine was also almost immediate – within 24 hours.

When the initial project included diazepam, and its placebo control equivalent, quotes were obtained for pricing for the diazepam and placebo. Bizarrely, the quick-delivered, conveniently-priced diamorphine was not in any way comparable to the pricing for diazepam. The quote we received was based on 12 diazepam capsules, with 24 identical placebo capsules and the total amount was four thousand, three hundred and fifty-one pounds, excluding VAT. The identical placebo capsules consisted of sucrose.

7.4.7 Meet your RNs, the Driving Force

Once ethics, MHRA and other local approvals had been received, the next step was to meet the research nurses (RNs) and the other clinical research facilities staff who would be involved in the study day to day. There were several meetings with potential research nurses. The career experience of research nurses is generally very varied, some have emergency medicine experience, others are mental health nurses by specialism. When explaining the details of the study to the research nurses, some of the nurses seemed surprised that such a study could go ahead, and others, for example, emergency nurses, were unfazed by the possibility to dealing with an emergency overdose situation, as they had seen many fatalities in their careers. It seemed that whoever the study was discussed with had a different expectation and understanding of the purpose of the study. It highlighted even further the importance of acquainting oneself with the people who would, in essence, be undertaking the day to day tasks of the study and upholding the integrity of the research.

7.4.8 Do Not Pass Go, Do Not Receive Green Light

Green light for recruitment is the final step that is required before the first participant can be recruited for the study. For this study, green light was obtained two months after the final approval was received. The reason for this delay was related to database validation. In all CTIMPs, there must be a specific type of database used throughout the study, one that is compliant with CTIMP rules and has very strict audit trail functions and enhanced security. The local Clinical Trials Unit has a fixed pricing system for their databases, which start at a minimum of £5,000, regardless of the number of participants. As this was not a realistic option, the opportunity arose to use a company that had recently been established as a user-friendly and regulatory approved database system. This required the database to be built by ourselves, from scratch, but was reasonably priced and as effective as other databases. Much of this was good news for the study, and despite the challenge faced in putting together a database from scratch, it was completed successfully. However, there was an aspect of the database usage in the trial that no one had envisaged, including the CRA herself. As the database was new, and had never been used previously by other trials in the Clinical Trials Office, there had to be a validation process. Unfortunately, the validation process could only be conducted by one member of the Clinical Trials Office - the database manager - who was part-time and overstretched. For this reason, green light could not be provided, and a waiting game was played (from September to November 2017). Again, this revealed the reality of undertaking a CTIMP.

Summary

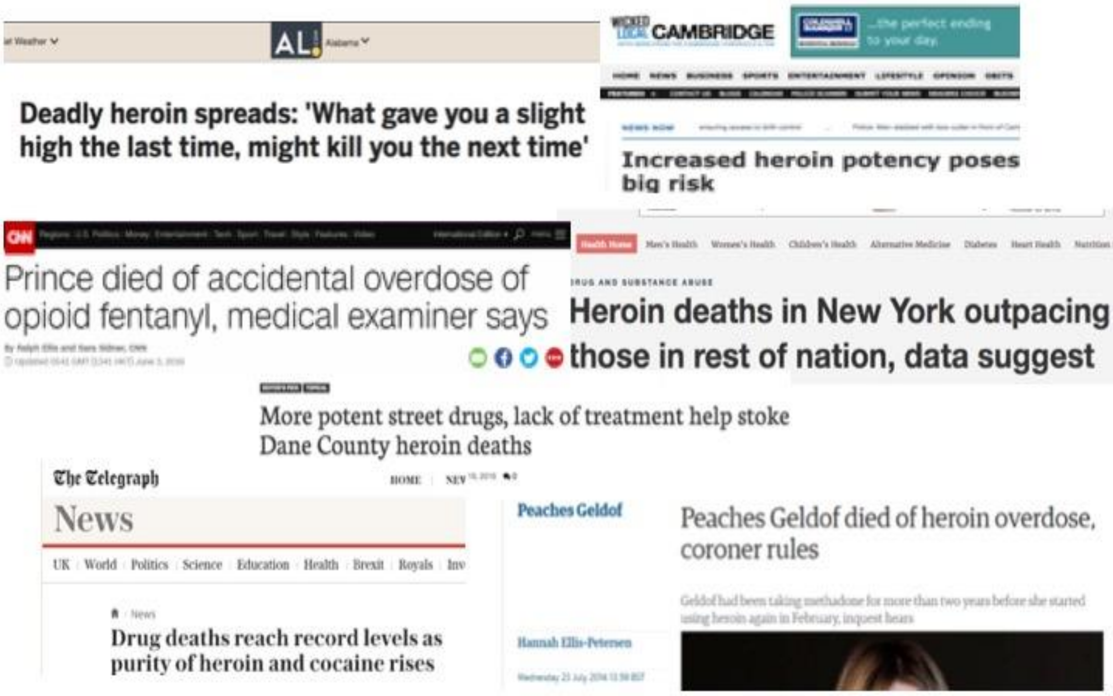
Preparation and development of these clinical trial protocols are generally time-consuming and lengthy and are required to comply to strict regulatory rules as well as adhere to upholding scientific value and rationale. Consultations were conducted with researchers and clinical colleagues, as well as service users. This chapter also delved into some of the clinical trial procedures that were involved in establishing the trial itself. It highlighted the reality of establishing a clinical trial, and the unexpected challenges that were experienced. In truth, studies that are not externally funded, such as this study, are not prioritised and administrative tasks are generally more delayed. These were obstacles that, unfortunately, occurred frequently and were mostly out of our control.

8 Heroin Overdose: Experimental Testing and Measurement in the Laboratory (AOO Study).

8.1 Preface

The concept of this study began at the initial commencement of my PhD studies. Risk factors and mechanisms of heroin overdose deaths have been discussed in detail in the earlier chapters of this thesis. As mentioned, there are many post-mortem examinations of overdose deaths that do not find particularly high levels of heroin. There also appear to be some cases where patients in heroin maintenance treatment experience significant changes in their physiological responses, despite being stable and tolerant.

These findings have led to the need to examine this further. Why is this happening when there is not technically an 'over'-dose? And yet 'over' doses and 'killer' batches of heroin that contain unusually high purity/dose are often identified as the cause of cluster of deaths in the community. Yet it is surprising that clusters occur if it is merely dose-related as one would expect the user community to adapt and reduce dose. Additionally, perhaps due to the celebrity persona associated with some of these deaths, there is also a great deal of media attention.


AL

Deadly heroin spreads: 'What gave you a slight high the last time, might kill you the next time'

CAMBRIDGE

Increased heroin potency poses big risk

CNN

Prince died of accidental overdose of opioid fentanyl, medical examiner says

Heroin deaths in New York outpacing those in rest of nation, data suggest

More potent street drugs, lack of treatment help stoke Dane County heroin deaths

The Telegraph

News

UK World Politics Science Education Health Brexit Royals

Drug deaths reach record levels as purity of heroin and cocaine rises

Peaches Geldof

Peaches Geldof died of heroin overdose, coroner rules

Hannah Ellis-Petersen

Figure 8-1: selection of newspaper headlines on heroin overdose and the influence of purity.

This confounding evidence consistently contributes to simplistic media reports which are often inaccurately reported, often embellished or simply false (Bammer, Ostini, & Sengoz, 1995; Darke et al., 1999).

Herein lays my first research question: Does more of the drug actually equate to more of a risk of overdose? To test this, we have, with ethical approval, given patients who were on a stable dose of diamorphine a small increment of 10% and 20% of heroin (i.e. a 110% or 120% dose) and observed a vast array of physiological responses, including airflow, oxygen, carbon dioxide and neural respiratory drive, and subjective responses of drug effect, drug liking and level of intoxication.

The data presented in this chapter took much preparation and the initiation of the study itself experienced many obstacles. The issues and preparatory work are presented in Chapter 7: Clinical Trial and Error. The data presented in this chapter are still being collated. Nevertheless, there is still a strong opportunity to reflect on the data collated thus far as this type of study is difficult to conduct but has far reaching implications.

I have presented the study methodology in this chapter at local and national meetings to colleagues in the Respiratory Medicine and Addictions fields. Some of the data in this chapter have been presented at a locally organised conference on Heroin on Trial in May 2018 and at the MRC Addiction Research Clinical Training Summer Meeting in July 2018.

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8.2 Introduction

8.2.1 Background

As mentioned in previous chapters, heroin and other opioids cause dampening on the regular breathing rhythm and respiratory drive. This can cause high levels of carbon dioxide (hypercapnia), low levels of oxygen (hypoxaemia) in the blood. A further complication of opioid overdose includes pulmonary oedema (accumulation of fluid in the lungs) (Leino et al., 1999; Pattinson, 2008; White & Irvine, 1999). It remains unclear why some people are more prone to experiencing hypercapnia and hypoxaemia than others.

It is received wisdom that purity is a risk factor for opioid overdose (Darke, 2014; Darke & Farrell, 2014). However, several issues relate to why this remains unclear and requires testing; firstly, street heroin is not consumed at doses, purities and frequencies that show any clear correlation with a heightened risk of overdose. This is evidenced by, a) toxicological examinations, and b) demographic reports. Great numbers of fatal overdose cases have low blood morphine (metabolite of heroin that is tested) concentrations, often similar to, or even below those of living intoxicated heroin users, or of heroin users who died from other causes (Darke et al., 2010b; Darke & Farrell, 2014; Davidson et al., 2003). Demographic reports reveal that fatal overdose is most common among long-term, dependent, injecting drug users, often over the age of 30 (Bauer et al., 2008; Darke, 2011, 2014; Degenhardt et al., 2011). This bears no relevance to the inexperienced and intolerant (to variations in purity) user that one might expect.

The idea that purity plays a role in overdose is blurred further when considering the opposing setting to this illicit drug market scenario, a heroin-assisted treatment clinic. Even where a pharmaceutical and titrated dose is administered, though rare, overdose events still occur (Oviedo-Joekes et al., 2009; Strang, Metrebian, et al., 2010) In the UK-based RIOTT clinic, the rate was reported to be around 1 in every 6,000 injecting events (Strang et al., 2010), and in the Canadian NAOMI clinic this figure was around 1 in 8,000 injecting event (Oviedo-Joekes et al., 2009). Clearly, respiratory depression can occur without variation in administered heroin doses. Previous work has shown that even regular doses of prescribed opioids show significant changes in oxygen saturation (blood oxygen level) (Dursteler-Mac Farland et al., 2000; Stoermer et al., 2003; Stohler et al., 1999). The onset and severity of respiratory depression is likely also affected by inter-subject variability and the factors underlying this susceptibility to overdose in certain individuals are poorly understood.

To test this in a clinical laboratory setting, a higher-than-regular dose was used as a comparative marker to address whether changes in dose (equivalent to changes in purity) truly does increase respiratory depression.

8.2.2 Objectives

The primary aim of the research is to address whether there are changes in physiological and subjective responses to varied doses of injectable heroin. Specifically, this study aims:

1: To investigate respiratory depression and hypoxaemic response to intravenous (IV) or intramuscular (IM) higher-than-regular doses of heroin as a marker for overdose.

2: To investigate effect of variations in IV and IM heroin dose on subjective and observer ratings of drug effect.

8.3 Methods

8.3.1 Trial Design

The study was a single-blind, dose escalation, within-subject design with four testing sessions. Each session was comprised of an intravenous or intramuscular injection of 100% OR 110% OR 120% of the regular dose of diamorphine. The following sequence of doses was self-administered (or administered by a doctor, if requested) with the patient blind to the dose on each study session:

1. Diamorphine=100% (IV or IM)
2. Diamorphine=110% (IV or IM)
3. Diamorphine=120% (IV or IM)
4. Diamorphine=100% (IV or IM)

Each session consisted of 30 minutes of pre-monitoring analyses (drug test, breathalyser and pregnancy test, if applicable), 30 minutes for preparing the participant for monitoring and 60 minutes of monitoring. Participants were not expected to remain at study facilities for longer than 120 minutes in total, per study day. However, in any case of adverse events, participants were not be discharged until symptoms were under control. There was a wash-out period of at least four days to ensure that there was no presence of excess metabolites. Between study visits, subjects were taking their treatment of diamorphine maintenance as per standard care. Additionally, after the trial ended, subjects were able to continue diamorphine maintenance treatment as per standard care.

Serial measurements of subjective drug effects and physiological responses were made prior to, and for one hour following, drug administration. A fourth session was implemented with the same dose as the first session to measure whether there were any effects on respiratory measures due to the novel laboratory setting.

Subjects on injectable diamorphine maintenance treatment, who were therefore on a stable titrated dose of diamorphine, were recruited for this study. As stated, a minimum of four days was the permissible window between study visits, and time from consent to first study session was a maximum time period of eight weeks.

8.3.2 Selection of Dose and Route

Subjects normally self-administer their diamorphine in separate doses throughout the day. Subjects were screened prior to the first testing, and during this process, the frequency and dosing pattern of the subject's usual daily dosing were established. For example, a patient who is on 300mg daily may take this in 3 equal parts, each consisting of 100mg doses or they may take it as a 1 x 120mg and then the remaining 60mg at night or many other patterns. The trial only examined one dose of diamorphine. This was determined at the screening visit. The affected dose was selected depending on circumstances of the individual patient. For example, where a subject was required to commute a longer distance to the CRF, it was more practical to affect their 2nd or 3rd dose of the day. In cases where the selected dose was not the first one of the day, subjects were asked to attend 4 hours after their previous dose. Diamorphine has a half-life of 2-3 minutes, but, because of the action of active metabolites such as morphine, its effects can last up to 3 to 4 hours (when injected), thus, the 4-hour time window was sufficient to prevent substantial interaction with the trial dose.

Where participants varied daily diamorphine dose, and/or where IV or IM routes were used interchangeably, the decision of dose and route was determined at the screening session, incorporating discussion between participant, research medic and treating clinician, as well as examination of peripheral venous access. A combination of these allowed suitable decision about route and dose, with preference given to IV over IM, where possible. IV was preferred because of the reliably complete level of absorption into blood and relevance to the wider field. Once the decision on route and dose had been defined, the same route and 100% diamorphine dose was kept consistent across all dose sessions.

8.3.3 Participants

Relevant patients (in this case, patients who are on an injectable diamorphine prescription) were approached by clinical care staff associated with the patient. Patients were based within selected services/clinics that provide a specified injectable diamorphine treatment for injecting heroin users. These were within South London and Maudsley NHS Foundation Trust (SLaM) and other allocated Participant Identification Centres (PICs). All potential participants received exactly the same standard treatment within their treating clinic. Potential participants were prescreened in the study site (Clinical Research Facilities; CRF) and all study procedures were also conducted at the CRF. All participants, whether within SLaM or within the PIC sites, continued with their normal treatment in between study sessions. Treating clinicians within the PIC site were updated upon participant consenting to take part in the trial. This was noted in the relevant site's patient system.

8.3.4 Pharmacy Procedures

Diamorphine Hydrochloride powder (freeze-dried powder in pharmaceutical ampoules) for solution for Injection (100mg or 500 mg, any brand allowed) was the Investigative Medicinal Product (IMP) for this study. A white to off-white, sterile, freeze dried powder of Diamorphine Hydrochloride BP for reconstitution for injection.

IMP dispensing was conducted by SLaM pharmacy. The diamorphine supplied for the purposes of this study was a licensed medicinal product that is available in the UK. Commercial stock was used for trial purposes. The IMP labelling complied with Eudralex Volume 4 annex 13 for the purposes of the trial. This was a single blind trial where dose was masked only to participant. This was conducted by making up each injection with water per volume to achieve same volume for each participant. All doses of diamorphine were made up to as close to a volume that the participant would normally use for their daily use, and was kept consistently for each session, thus preventing participants from being aware of what dose they were given. Two non-blinded nurses were required to bring the medication to the patient (the medication was stored and dispensed by the Maudsley Hospital pharmacy) and were responsible for preparing the diamorphine and supervising the self-administration of the injectable diamorphine.

Diamorphine at 100% of the participant's regular maintenance dose was used for the regular dose condition, 110% and 120% of the participant's maintenance dose was used for the 110% and 120% dose condition, respectively. Doses were prescribed for each session separately.

8.3.5 Study Procedure

Chapter 4 (Methods) highlights the methods for this study in detail. Essentially, each session consisted of 30 minutes of pre-monitoring analyses (vital signs, SpO_2%, drug test, breathalyser, and pregnancy test, if applicable), 30 minutes of preparing the participant for monitoring and 60 minutes of monitoring. Serial measurements of subjective drug effects and physiological responses were made 3 minutes prior to, and for 60 minutes following drug administration. Participants were not expected to remain at study facilities for longer than 120 minutes in total, per study day. This time was prolonged if adverse events occurred.

Diamorphine was self-administered intravenously or intramuscularly on the study day. Participants were encouraged to self-administer the diamorphine in under 1 minute, and timing of diamorphine administration was measured by video by one of the trial staff. Delegated trial staff (nurse or doctor) was available for assistance, and also, if the patient chose not to self-administer, a delegated trial staff member could administer the diamorphine (nurse or doctor administration).

8.3.6 Outcomes

Table 8-1 details the primary physiological outcome measurements that were taken during the study sessions. Please see Full Study Flowchart and Study Procedures by Visit for full list of procedures on the four study days in Appendix E-2.

Table 8-1: Outcome measurements

Assessment	Outcome Measurement	Device	Timing
Ventilation	Respiratory rate (V_f), tidal volume (V_t) and minute ventilation (V_e)	Pneumotachograph connected to a Hans Rudolph mask	continuous recording
Pulse oximetry	Average and minimum SpO_2%	Finger-clip oximeter	continuous recording
End-tidal carbon dioxide	Average and maximum of peak %CO_2 per expired breath ($ETCO_2$%)	Pneumotachograph (with catheter on pneumotach) & capnograph	continuous recording
Electromyography (parasternal intercostal muscles)	Neural Respiratory Drive: EMG_{para}%max & EMG_{par}a%index (see methods: (Murphy et al., 2011; Reilly et al., 2013; Reilly et al., 2011))	Surface electrodes and biomedical amplifier	continuous recording
Transcutaneous blood gas meter	Average and maximum $TcCO_2$	Ear lobe sensor	continuous recording

8.3.7 Assessments at Each Visit

Table 8-2 displays the tasks that occurred during the three main stages of the study.

Table 8-2: assessments at screening and at each study visit.

Assessments at each visit

Screening Visit	Pre-testing on Study Day	During Study
Informed consent	Assessment of changes to medication/health (concomitant medications, adverse events)	Vital signs
Demographics, Medical History & height & weight (BMI)	Pregnancy status/test (females)	Airflow and $ETCO_2$% (via face mask and pneumotach)
Spirometry	Breathalyser for alcohol	EMG_{para} (via sticky pads on top of chest)
SpO_2% (via finger pulse oximeter)	Drug screen	$TcCO_2$ (via earlobe sensor)
Vital signs	Full eligibility confirmation	SpO_2% (via finger pulse oximeter)
Pregnancy Status/Test (Females)	Vital signs	Pupil size
Concomitant medication check	SpO_2% (via finger pulse oximeter)	Subjective, and staff rating of, drug effects (via VAS response scale and GCS)
Eligibility Assessment	Pupil size	Adverse Events check

8.3.8 Indicators of Significant Respiratory Depression

The following indices of significant respiratory depression were recorded and used as evidence for respiratory depression:

- SpO_2 of <80%; <90% for longer than 10 seconds,
- $ETCO_2$% per breath exceeding 6.5%,
- absence of inspiratory airflow and/or parasternal intercostal muscle EMG activity for more than 10s (apnoea),
- absence of response to verbal stimuli.

Further criteria were also recorded and assessed for severity of respiratory depression:

- frequency dips of SpO_2<90% longer than 10seconds,
- % time spent SpO_2 <90% across the 60mins,

- frequency of breaths above 6.5% for $ETCO_2$% and 6.6kPa for $TcCO_2$ (equivalent to 6.5%) for each time point,
- % of time spent over 6.5% over 60mins,
- frequency of pauses that were longer than 10 seconds. This value will be multiplied by 60 to produce the Apnoea Hypopnea Index (AHI) for each time point. A value per hour,
- Frequency of pauses that were longer than 10 seconds,
- % changes from baseline to peak or nadir for each of the measures.

8.3.9 Drug Effect Measurements

At 3 minutes prior to administration of the injectable diamorphine, and then at 0, 3, 8, 15, 30 and 60 minutes participant were asked to rate their subjective strength of drug effect, drug liking and sedation using a visual analogue scale (VAS) (Nicholson, 1978). At these times pupil size was recorded, and a staff rating of level of consciousness (eye, verbal and motor responses as in the Glasgow Coma Scale (Teasdale & Jennett, 1974)) and intoxication were also documented using a VAS (previously used by: Comer et al., 2008; Kelly et al., 2005; Lintzeris et al., 2007; Sessler et al., 2002).

8.3.10 Sample Size

This study received ethical approval for 12 subjects, but there are only data available for three subjects in this thesis. The sample size of 12 is small study, but this is an exploratory study for which a power calculation was deemed not to be required. Studies of this type have typically used sample sizes close to this number by utilising design of repeated measures with the same subjects, thereby obtaining strength from within-subject trial design. For example, sample sizes of n= 4 to 12 (Dowling et al., 2008; Lintzeris et al., 2006; Lintzeris et al., 2007; Walsh et al., 1994; White et al., 2009). Measuring variations between individuals would involve a much larger study which is beyond the scope of this trial, and would not be without risk to the participants involved.

8.3.11 Blinding

The study incorporated a single-blind, dose escalation design with four testing sessions. This design was deliberately chosen to ensure safety with increasing doses of diamorphine, with explicit decision that the sequence of the study sessions were not randomised. Furthermore, due to the regulations on diamorphine prescribing, i.e. that it cannot be prepared beforehand and that two healthcare professionals (e.g. two nurses) must be present, masking the research team members was not possible. However, in order to reduce expectation bias, participants were not informed of which dose they were self-administering. The drug was prepared by nurses and masked by making up to the same volume with water. Consequently, the same volume was self-administered by the participant on each of their four dose sessions and was thereby blinded to the true dose.

8.3.12 Statistical Method

The statistical aspects of the research were reviewed by a statistician (Dr Elizabeth Ryan) within the Institute of Psychiatry, Psychology & Neuroscience. The outcome measures were calculated offline and used for analysis. Friedman's test was used to test for differences between baseline, minimum/maximum or successive time-points for each measure after drug administration (Friedman's statistic, Q). In addition, post hoc analysis was conducted using Dunn's Multiple Comparison Test. Where there were missing data, differences between diamorphine dose condition (100% versus 110% versus 120% of the daily maintenance dose) was tested using the Wilcoxon Signed Rank Test (W-score) for each paired dose session (e.g. 100% versus 110%).

8.3.13 Recording of Injection

An anonymised video (with consent from the participant) was taken of the administration procedure. The purpose of this was to accurately relay the timing of injection, until plunger is pushed down all the way. The number of seconds that this process took was recorded after the study using the video as a guide.

8.3.14 Brief Informal Interview

At the end of each visit, participants were briefly asked about how the experience was, and whether the session and drug experience felt any different from the previous visits or from their usual experience. They were also asked about what dose they thought they had received. This was more of an informal dialogue between researcher and participant but was noted for each participant in their study notes. This was in the form of a 'check-out' process at the end of each visit.

Figure 8-2: Clinical Research Facility.
These two figures illustrate the setting in which the studies took place. This was within a clinical room of a clinical research facility, within a large teaching hospital.

8.4 Results

8.4.1 Participants & recruitment

Recruitment began in January 2018 after green light for recruitment was granted. Data collection for the data presented in the thesis occurred between February 2018 and August 2018. Three participants were screened, and all three were included in the study. With one exception, all participants attended all four visits. For one participant, the study team decided that a 20% dose increment was not appropriate, and unsafe due to the length of apnoeic episodes and shallow breathing (low tidal volume) observed during session two, the 120% dose session (session 3) was omitted and the sequence progressed directly to session 4, i.e. the final study at 100% dose. The results will be presented case by case initially and then overall group results will be described by measure.

8.4.2 Demographics & Screen

All three participants were male and had a similar age of 62, 63 and 59 years (Table 8-3). All three had a BMI in the normal range (19.6, 19.3 and 24.8 kg/m^2). One participant was prescribed a dose of 30mg diamorphine that was injected IV or IM, once daily. The second participant had a prescribed dose of 400mg diamorphine that was injected three times IM daily, and on occasion, IV. The third participant had a prescribed dose of 630mg diamorphine that was injected IM, three to four times daily. Two of three participants were also prescribed doses of 450mg and 360mg morphine sulphate (MST) that was taken as an oral dose daily. Except for one participant who self-reported regular use of cannabis oil, none of the participants reported use of alcohol or other illicit drugs. Urine analysis and breathalyser results on the day of each study session confirmed absence alcohol and other drugs.

Two of the three participants had diagnosed chronic obstructive pulmonary disease (COPD), and a third had spirometry results and history that was compatible with COPD with a FEV_1 level (65.8%) that would indicate a moderately-severe category of COPD. Two participants had hypertension. One participant was Hepatitis C positive and was being treated by a combination of antiviral medication (Ribavirin, Viekirax and Dasabuvir) at the time of the study and another participant had very recently cleared Hepatitis C.

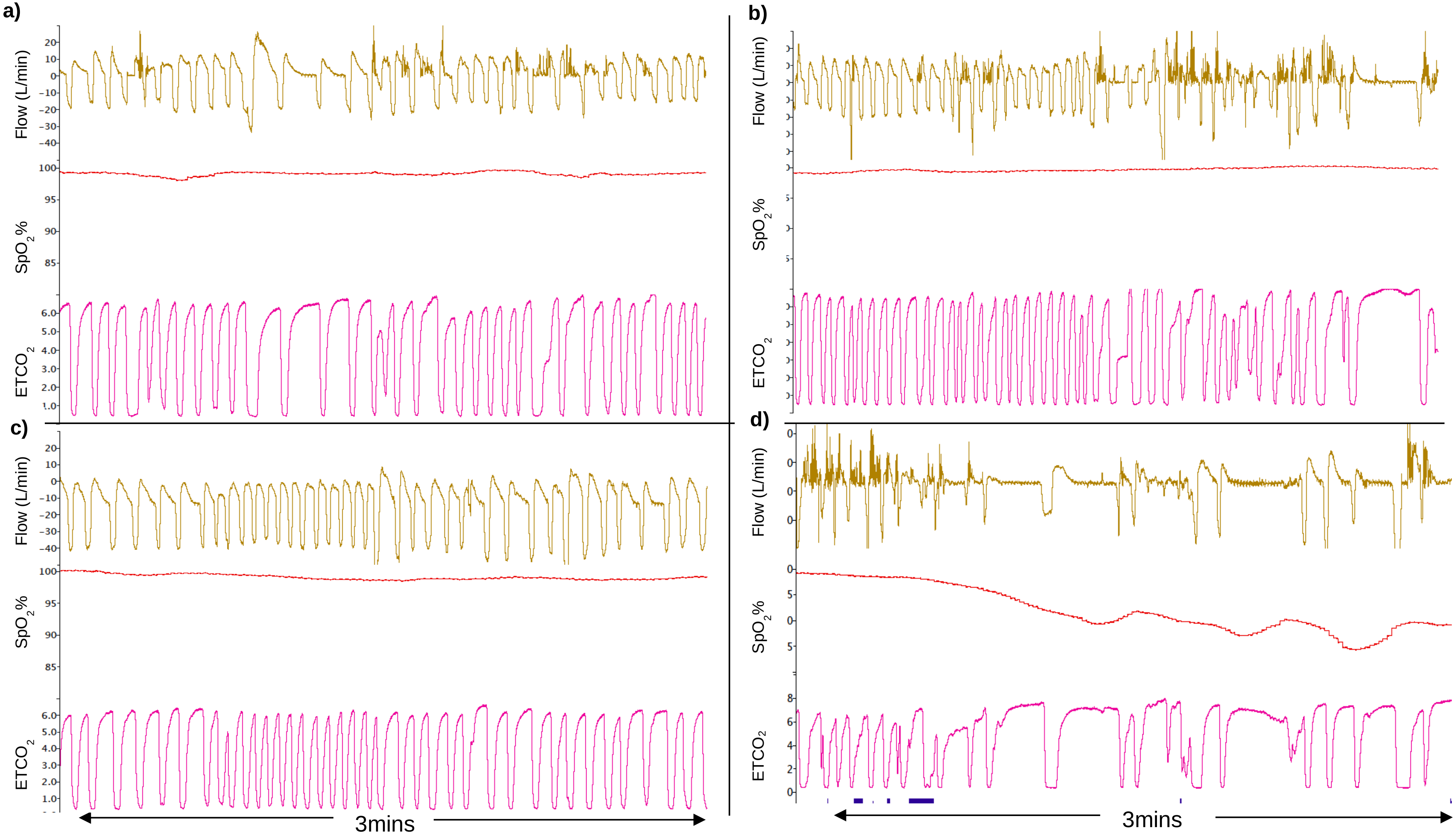


Figure 8-3a-d: A sample recording from Participant B. All boxes display airflow on the top trace, oxygen saturation in the middle trace and end-tidal carbon dioxide at the bottom and all are across 3 minutes.
a) and b) 100% dose session of 100mg diamorphine, administered by study doctor, a) baseline (-3minutes) and b) 2 minutes post diamorphine administration. c) and d)110% dose session of 110mg diamorphine, administered by study doctor, c) baseline (-3 minutes) and d) 2 minutes post diamorphine administration.

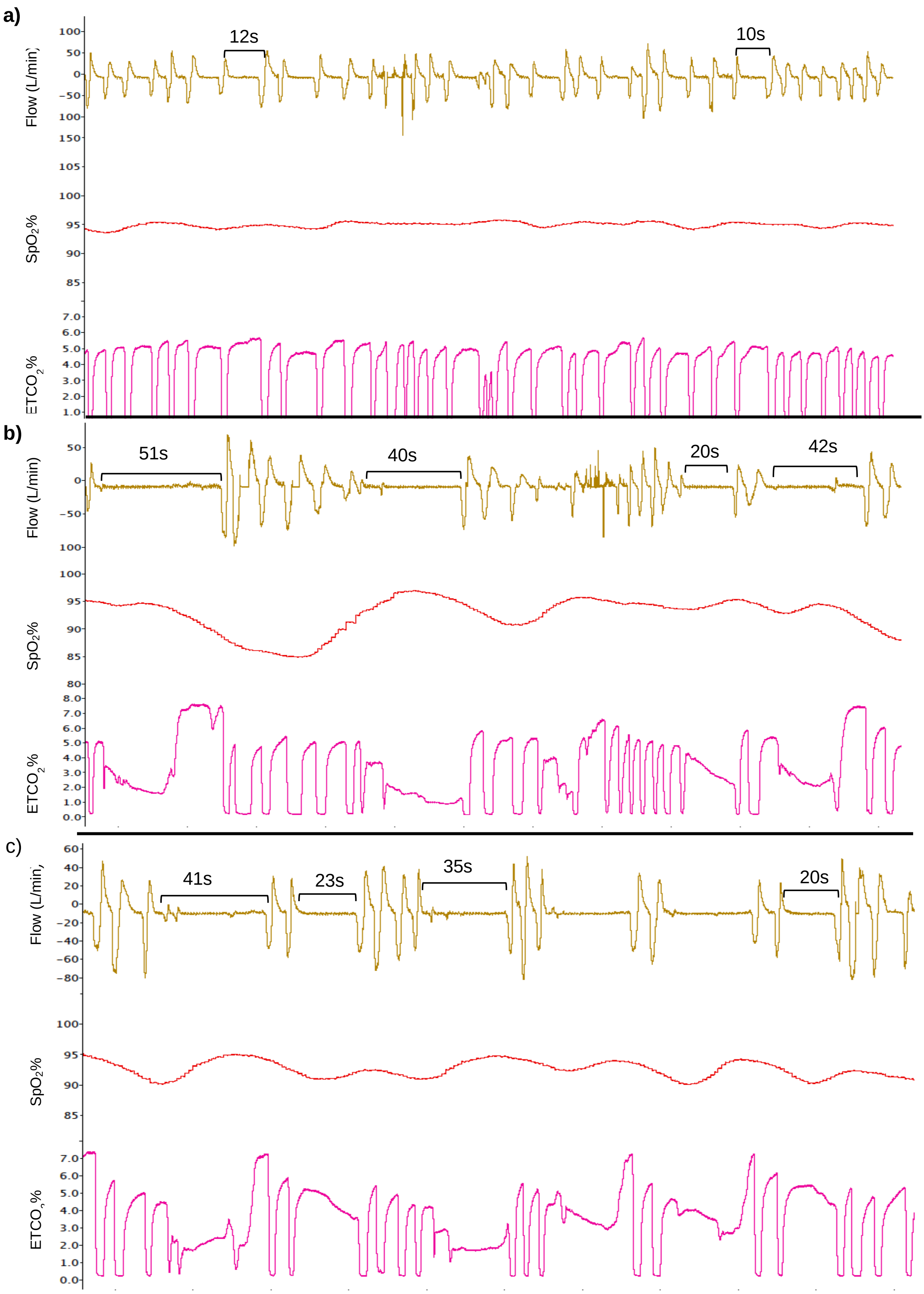


Figure 8-4a-c: A sample recording from Participant A in the same 100% dose session.
All boxes display airflow (brown), oxygen saturation (red) and end-tidal carbon dioxide (pink) and are all across 5 minutes of recording. a) 5 minutes baseline; b) 5 minutes post diamorphine administration; c) 55 minutes post diamorphine administration. Apnoeic episodes are indicated (seconds) on the flow trace.

8.4.3 Case 1

Participant A is male with a 45-year injecting heroin use history. He started diamorphine maintenance treatment 12 years ago as part of RIOTT. The participant was reduced to 30mg four years ago and his previous dose was 150mg diamorphine daily. A standard week of use involves some days that may be higher in dose than others. However, if using IM, this dose increases to 50mg but his current IV dose was never more than 30mg on each administration. The route for the study was IV and dose was 30mg. This participant did not report use of any other drugs, including alcohol or benzodiazepines but did describe a previous history of alcohol use disorder. Results for participant A are displayed in Figure 8-5a-g.

SpO_2%: Participant A showed an average SpO_2% of 93.6% across all doses, and a minimum SpO_2% of 84.3% in the 100% dose session (similarly with the increased dose sessions, the minimum value was 84.6% and 84.9%). Participant A showed a percentage change from baseline of between 12.4% and 10% with the greatest drop in SpO_2% being observed in the 120% dose session. There was no significant difference between doses ($Q=3.9$, $p=0.3$). SpO_2 reached below 90% for longer than 10 seconds in every dose session for this participant. The percentage time spent under 90% across the 60 minutes of monitoring was 2.5%, 10.1%, 10%, 13.9% in the four dose sessions, respectively.

$ETCO_2$%: Participant A observed varying averages of $ETCO_2$ across the different dosing sessions with a range of 6.5% to 5.7%. The highest level was seen in the first 100% dose session. Further, a 2.9% average change from baseline to peak $ETCO_2$% was observed, with the highest % increase in CO_2 occurring in the 120% dose session. In terms of frequency of breaths above 6.5%, rates of 3.7, 1.4, 1.9 and 0.7 breaths per minute above 6.5 in the four dose sessions, respectively were observed. Additionally, percentage of total breaths above 6.5% over the 60 minutes of monitoring started at 45.1% in the first 100% dose session and dropped considerably to 13.6%, 19.3% and 9.2% in the three subsequent dose sessions, respectively. Overall, there were significant differences between doses ($Q=15$, $p=0.002$), with significantly lower levels of $ETCO_2$% being observed in the 110% and repeat 100% dose sessions ($p= 0.003$ and $p=0.02$, respectively).

$TcCO_2$: Participant A had a range $TcCO_2$ between 5.9kPa to 6.4kPa with the highest being observed in the first 100% dose session. Participant A showed the greatest change from baseline in the 110% dose session (18%) and the smallest change (6%) was seen in the first 100% dose session. There was a significantly lower level of $TcCO_2$ in the repeat 100% dose session compared to the first 100% session (Q=11.8, p=0.008).

NRDI: Participant A showed an average range of between 77.7min^{-1} and 109.1min^{-1} with the highest level being observed in the 120% dose session. Participant A initially exhibited a 26.7% reduction in drive from baseline to post-administration nadir. This change was at a lower magnitude in the repeated 100% dose where a reduction of 11.8% was seen. The two dose increases showed slightly greater reductions of 35% and 30.5% in the 110% and 120% dose sessions, respectively. Overall, differences between the doses were significant (Q=13, p=0.004), with a 20% increase in dose showing significantly higher levels of NRDI compared to both the 100% and 110% dose sessions (p=0.02 and p=0.006, respectively).

Ventilation: Participant A showed a minimum respiratory rate of 5 breaths/minute in the repeat 100% and an average of between 7.7 and 10.5 breaths/minute. The rate did not exceed 11.7 breath/minute. Significant differences were observed across doses (Q=18, p=0.0005), with the 10% dose increase showing a significant decrease compared to the two 100% dose sessions (p=0.006 and p= 0.003). Tidal volume remained between 0.3L and 1.6L and was highest in the 120% dose session and significantly higher than usual dose (Q=11.2, p=0.006). Minute ventilation remained between 2L/min and 16.6L/min and again, was highest in the 110% and 120% dose session which were both significantly higher than the usual dose (p=0.02 and p=0.003, respectively).

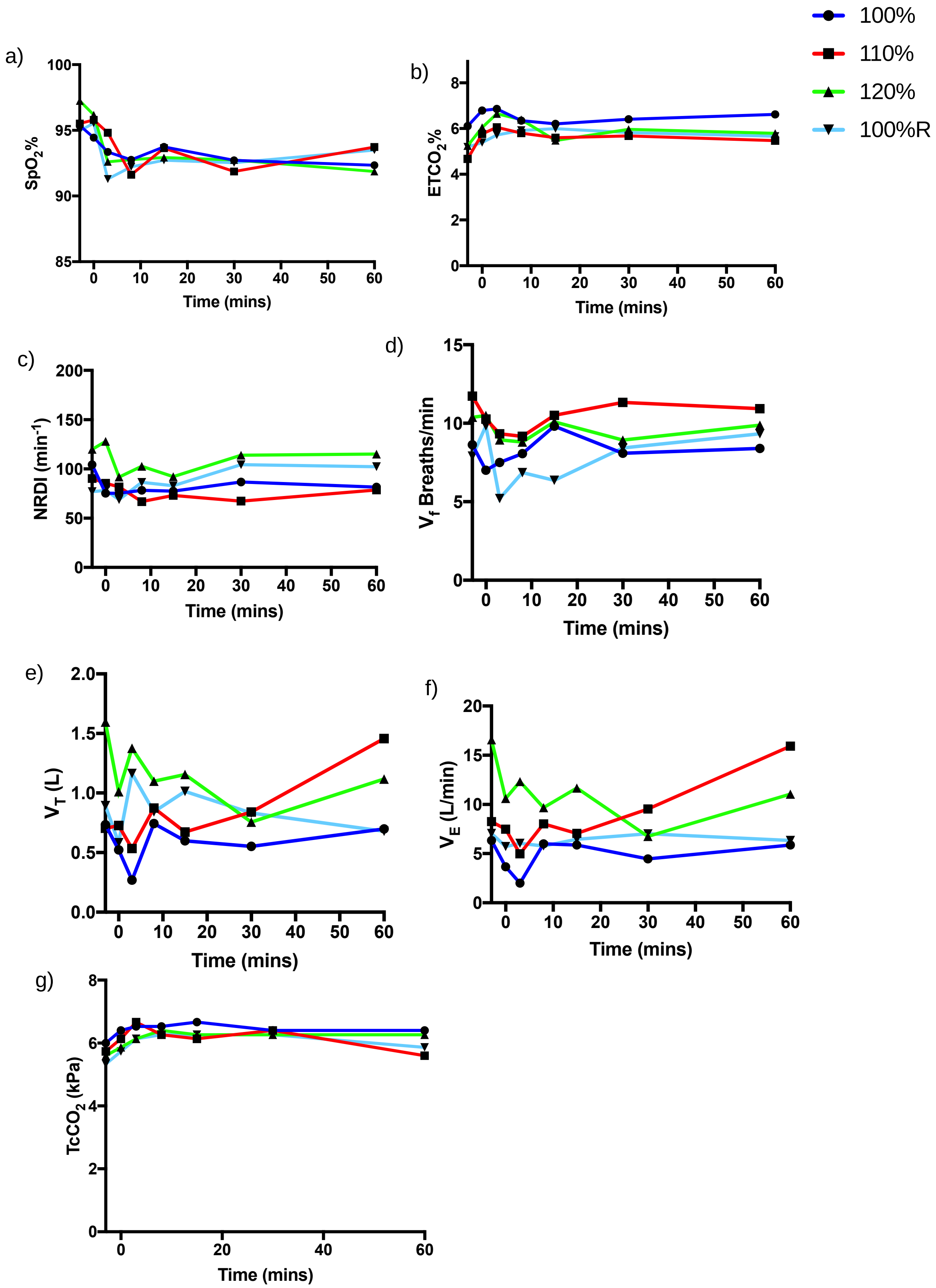


Figure 8-5a-g: Participant A one-minute averages for each dose session - 100% (dark blue); 110% (red); 120% (green) and 100%R (light blue): a) SpO_2%; b) $ETCO_2$%; c) NRDI; d) Vf respiratory rate; e) VT Tidal Volume; f) V_E Minute ventilation; g) $TcCO_2$.
SpO_2% = oxygen saturation; $ETCO_2$% = end-tidal carbon dioxide; NRDI = neural respiratory drive index; $TcCO_2$ = transcutaneous carbon dioxide.

8.4.4 Case 2

Participant B is male and a predominantly intramuscular heroin user with a 38-year use history. Participant B used heroin once when 18 years old and became dependent in early/mid-1980s using Pakistani heroin by chasing and moved onto IV heroin in early 1990s. He was started on a diamorphine prescription in 2006 with occasional supervision. His dose increased to the current dose of 300mg daily in 2010 and has been on same dose since. In 1990s, he had several overdoses and believed that on two occasions it was related to heroin of greater strength than he knew and on one occasion when he had mixed heroin with alcohol. He only drinks minimally now but can smoke cannabis up to 10 joints per day.

When he used to take IV and IM, he would usually take the same dose, i.e. there was no dose adjustment for different route. His current routine is 100mg IM in early morning, 100mg an hour later and 100mg in the evening. On weekends, he receives a 3-day supply and sometimes has used 400mg, 450mg or even 500mg on a Saturday and then as little as 100mg on the remaining days. He does not use more than 100mg as his occasional IV diamorphine dose. For the study IV dose of 100mg was chosen. Results for Participant B are displayed in Figure 8-6a-g.

SpO_2%: Participant B showed an average of 95.5% and 96.6% across all dose sessions, and a minimum of 84.3% being observed in the 110% dose sessions. The % change from baseline was between 6% and 14.8%, with the greatest change being observed in the 110% dose session. SpO_2 reached below 90% for longer than 10 seconds in the 110% dose session. Percentage time spent under 90% over the 60 minutes of monitoring in this dose session was 4.4%. There were no significant differences between doses ($Q=1.1$, $p=0.6$).

$ETCO_2$%: Participant B had an average of peak per breath of 6.7% and a maximum level of 9.1% in the 110% dose session. A change from baseline average of 2% with the highest change being at the 110% dose session of 2.9%. There were also differences noted in the % of breaths above 6.5% across the 60 minutes of monitoring. In the first 100% dose session, Participant B showed an average rate of 5.4 breaths per minute above 6.5%, which was 70% of all breaths over the 60-minute monitoring period. In the 110% dose session, Participant B

showed an average rate of 4.9 breaths per minute above 6.5% which is equivalent to 56% of breaths across the 60-minute period. Finally, in the second 100% dose session, a lower level of 3 breaths above 6.5% per minute was observed. This was equivalent to 34% of all breaths in the 60-minute monitoring period. Overall, however, there were no significant differences between the doses (Q=4.6, p=0.1).

$TcCO_2$: Participant B had a range $TcCO_2$ between 5.5kPa to 6.4kPa with the highest being observed in the first 100% dose session. Participant B showed the greatest change from baseline in the 110% dose session (21%) which was also the highest change amongst all participants for $TcCO_2$. Overall, there was a significantly different level of $TcCO_2$ between doses (Q=9.5, p=0.005) with a higher level in both 100% and 110% dose session compared to the repeat 100% dose session (p=0.02, p=0.04, respectively).

NRDI: The average values for NRDI in the two dose sessions are 118.5 min^{-1} and 133.6min^{-1} (100% and 110%, respectively). Participant B showed a 107% reduction in drive from baseline post-drug administration in the 100% dose session, and a less pronounced 63.3% reduction in the 110% dose session. A significant electrical noise issue led to difficulty in analysing the EMG_{para} recording in the repeat 100% dose, thus, the level of NRDI could not be attained for this dose session. There was no significant difference between the two doses for NRDI (W=20, p0.1).

Ventilation: Participant B showed the highest respiratory rate in the 110% doses session (11.4 breaths/minute) and an average between 7.7 and 8.8 breaths/minute across all sessions, there were no significant differences between doses (Q=2, p=0.5). Average tidal volume remained relatively equal at 0.3L to 0.2L across all sessions with the highest tidal volume reaching 0.5 in the first 100% dose session and a significantly lower tidal volume was seen in the repeat 100% dose session compared to the first 100% dose (Q=8.9, p=0.01). Minute ventilation was similar with an average range of 2.3L/min to 1.7L/min and a maximum level of 4.7 seen in the first 100% dose session, but none of the doses showed any significant differences (Q=6, p=0.05).

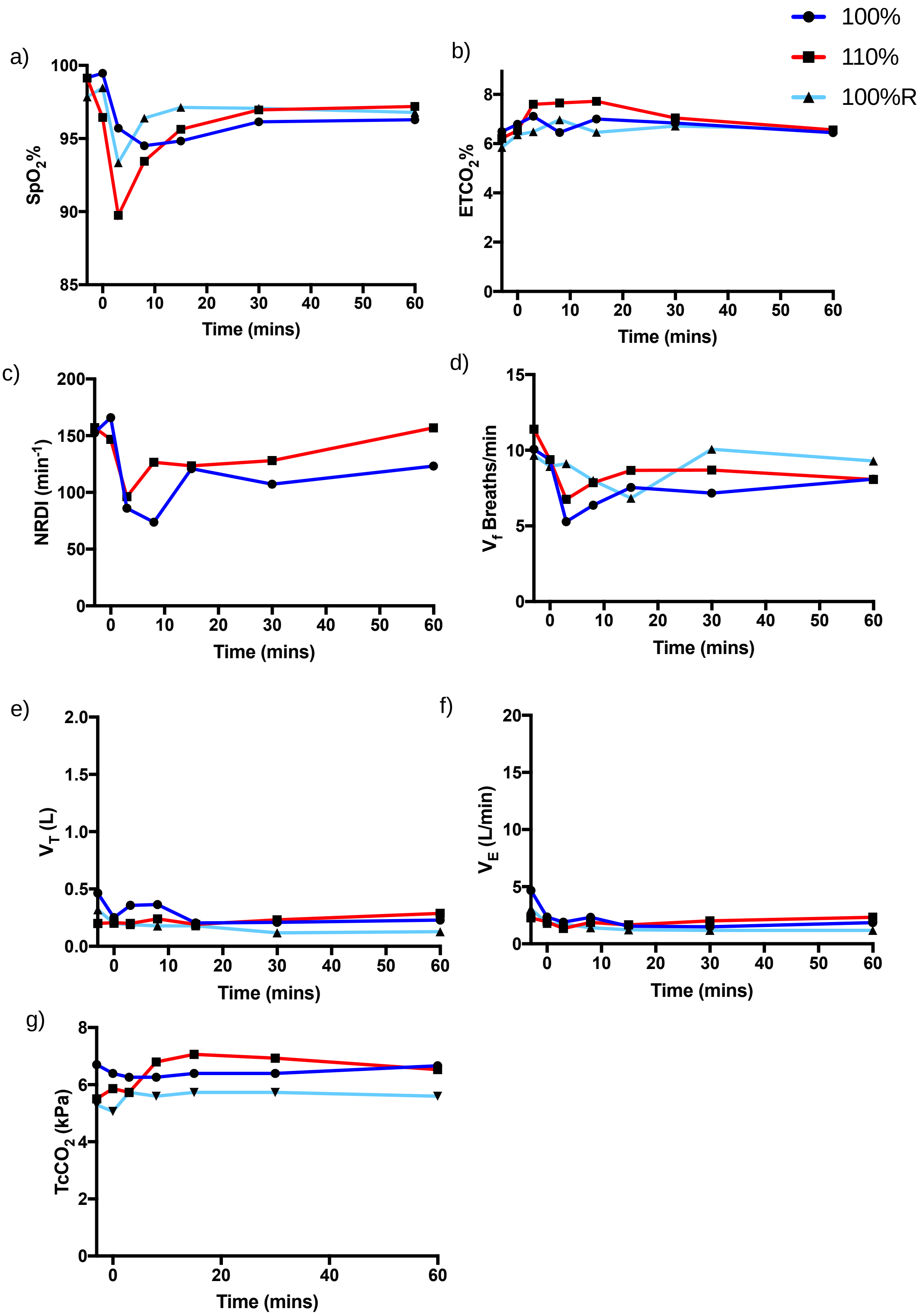


Figure 8-6a-g: Participant B one-minute averages for each dose session - 100% (dark blue); 110% (red); 120% (green) and 100%R (light blue): a) SpO_2%; b) $ETCO_2$%; c) NRDI; d) respiratory rate; e) Tidal Volume; f) Minute ventilation; g) $TcCO_2$.
SpO_2% = oxygen saturation; $ETCO_2$% = end-tidal carbon dioxide; NRDI = neural respiratory drive index.

8.4.5 Case 3

Participant C is male with a 30-year heroin-using history. His current prescription is 630mg daily, which is taken 200mg IM, occasionally IV in the morning, then 200mg in the afternoon, then 200mg in the evening and the final 30mg before sleep. He does not alter the dose when administering IV but only does this when a vein is accessible. In the study, peripheral venous access was deemed unsuitable and thus, IM with 200mg was chosen. This participant did not report the use of other drugs, including benzodiazepines and alcohol. Results for Participant C are displayed in Figure 8-7a-g.

SpO_2%: Participant C showed an average of 95.3% and 96.1% across the dose sessions and a minimum of 92% observed in the 110% dose session. Participant C showed comparatively minimal % change of between 3.1% and 3.5% from baseline to nadir compared to the other two participants. This participant did not experience any dips of SpO_2% below 90% for longer than 10 seconds. There were no significant differences between doses (Q=3.5, p=0.3).

$ETCO_2$%: Participant C had an average of 6.6%, 6.1%, 6% and 6.4% $ETCO_2$% across all dose sessions with the highest level being observed in the first 100% dose session. A change from baseline to peak $ETCO_2$% of 1.2% to 1.9% was observed. With regard to the frequency of breaths above 6.5% across the 60-minute observation period, 4.6, 1.4, 1.7 and 4.7 breaths per minute were observed. The % of total breaths above 6.5%, the figures were as follows 43%, 13.6%, 15.5% and 45.8% in all of the dose sessions, respectively. Overall, there were significant differences between the doses (Q=17, p=0.0006), with the 10% and 20% increased doses showing a significantly lower level of $ETCO_2$% compared to the 100% dose sessions (p=0.01 and p=0.006).

$TcCO_2$: Participant C had a range $TcCO_2$ between 5.5kPa to 6.4kPa with the highest being observed in the first 100% dose session. Participant B showed the greatest change from baseline in the 110% dose session (21%) which was also the highest change amongst all participants for $TcCO_2$. Overall, there was a significantly different level of $TcCO_2$ between

doses (Q=18.4, p=0.0004) with a lower level in both 120% and repeat 100% dose session compared to the first 100% dose session (p=0.003, p=0.006, respectively).

NRDI: Participant C showed an average of NRDI between 65 min^{-1} and 71.4min^{-1}, with the lowest level of drive being observed in the 120% dose session (51 min^{-1}). This participant also showed an 80.1% reduction from baseline to nadir post-dose in the first 100% dose session. Each dose increase appeared to show less of a reduction than the initial 100% dose session, with 61%, 44%, 39% respectively. Overall, significant differences were observed between doses (Q=15, p=0.002), with a 20% dose increase showing significantly lower levels of NRDI compared to usual dose and a 10% increase.

Ventilation: Participant C showed the highest respiratory rate in the 120% dose session (13.4 breaths/minute) and an average range of 10.2 to 11.1 breaths/minute). There were no significant differences between doses. Tidal volume was on average between 0.9L and 0.3L with the lowest tidal volume being observed in the 120% dose session (and was significantly lower than usual dose, p=0.003). The repeat usual dose also showed a significantly lower level of tidal volume than the first usual dose (p=0.01). Minute ventilation (V_E) was observed to be between 0.8L/min and 2.9L/min on average, with the lowest V_E being observed in the repeat 100% dose session (session 4), which was significantly lower than the first usual dose (p=0.006). The 120% dose session also showed a significantly lower level of minute ventilation compared to the 100% dose session (p=0.01).

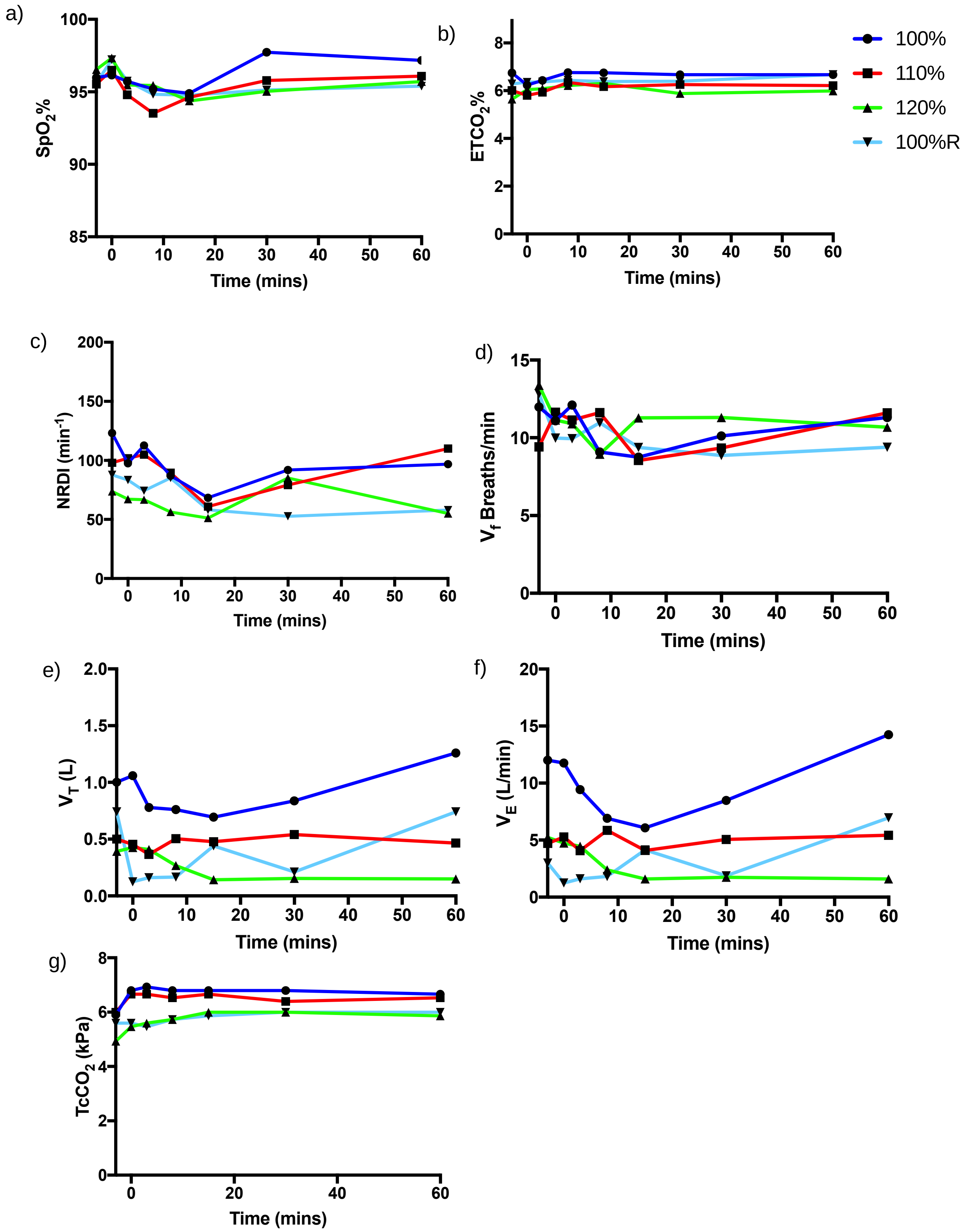


Figure 8-7a-g: Participant C one-minute averages for each dose session - 100% (dark blue); 110% (red); 120% (green) and 100%R (light blue) a) SpO_2%; b) $ETCO_2$%; c) NRDI; d) respiratory rate; e) Tidal Volume; f) Minute ventilation; g) $TcCO_2$.
SpO_2% = oxygen saturation; $ETCO_2$% = end-tidal carbon dioxide; NRDI = neural respiratory drive index.

Table 8-3: Demographics and other clinical details for each of the three participants.
BMI=Body Mass Index; MST= Morphine sulphate; COPD= chronic obstructive pulmonary disease; FEV_1%predicted= % predicted of Forced Expiratory Volume in 1 second; VC% predicted= % predicted of Vital Capacity.

Pt #	Age	BMI (kg/m^2)	Usual dose (mg)	Usual route	Other opioids (mg)	Other prescribed medication	Use of illicit drugs	Comorbidities	FEV_1 %pred	VC %pred	Injected	Speed of inject (secs)
1	62	19.6	30	IV or IM	MST (450mg)	Zopiclone (7.5mg)	None	COPD (diagnosed), hypertension	64.4	86.0	Self	1) 5 2) 6 3) 5 4) 6
2	63	19.3	300	IM, occasionally IV	None	None	Cannabis oil	COPD (diagnosed), hypertension	77.3	91.9	Doctor	1) 4;direct IV 2) 12;cannula 3) 4; cannula
3	59	24.8	630	IM	MST (360mg)	Hep C antivirals	None	Hep C, COPD	65.8	84.2	Self	1) 6 2) 5 3) 5

8.4.6 Primary Outcomes by Measure (Aim 1)

The focus for this section will focus on two overarching aspects: the observations within and between subjects, and amongst these the observations within and between different doses. The data are presented in the first instance by each respiratory measure separately.

8.4.6.1 Oxygen Saturation (SpO_2)

The average SpO_2% varied between 89.7% to 99.47% across all participants and doses (Figure 8-8a-d). Overall, there were significant differences from baseline to successive time points across all subjects (Q=35, p-0.0001), with levels at 3- (p=0.01), 8- (p=0.0003) and 15-minute (p=0.01) time points significantly lower compared to baseline. There was no significant difference between doses (100%v110%=-69,p=0.2; 100%v120%=-7,p=0.9; 100%v100%R=-47,p=0.4). Figure 8-8a-d shows the median values for each dose and the individual plots.

None of the participants in any dose session displayed a dip below 80%, however, the average SpO_2% for all participants was below 96% in all of the dose sessions. One of the three participants reached below 90% SpO_2 for longer than 10 seconds in every dose sessions, and another reached this criterion in one dose session.

The % oxygen desaturation from baseline in each session varied somewhat from 3% to 14.8% change in SpO_2% from baseline to nadir. On average, the 110% dose session showed a greater change compared to other sessions, and also had the overall largest change from baseline (14.8%).

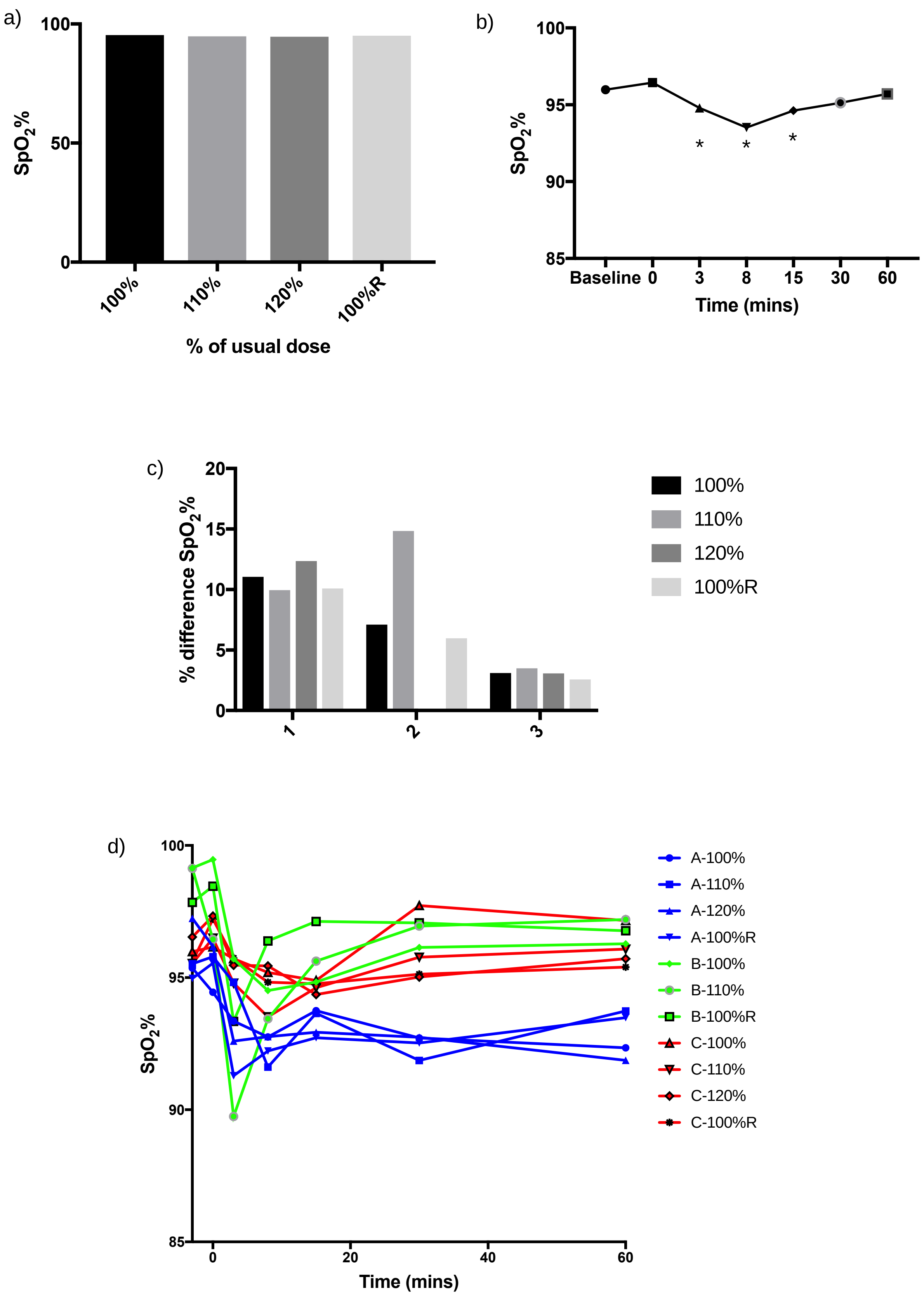


Figure 8-8a-d: SpO_2% results.
a) median values for each session for all participants; b) one-minute averages of SpO_2% for all participants at baseline (-3 minutes), 0, 3, 8, 15, 30 and 60 minutes after diamorphine administration; c) one-minute averages of SpO_2% for each individual participant; d) % desaturation from baseline for each participant and dose session. SpO_2% = oxygen saturation; 100%R = repeat 100% dose. Participant A = 1; Participant B = 2; Participant C = 3 *$p<0.05$

8.4.6.2 End-Tidal Carbon Dioxide ($ETCO_2$)

Across all participants and doses the average of the peak $ETCO_2$ per breath was between 5.98% and 6.6% (Figure 8-9a-d). Overall, there were significant differences from baseline to successive time points (Q=23.8, p=0.0006), with levels significantly higher in the 3- (p=0.02), 8- (p=0.0005) and 15-minute (p=0.03) time points (all $p<0.05$). $ETCO_2$% was significantly lower in the 110% (W=-139, p=0.01), 120% (W=-103, p=0.0002) and the repeated 100% (W=-185, p=0.024) dose session compared to the first 100% dose session.

$ETCO_2$% per breath was above 6.5% in all participants in all of the dose sessions. The % change from baseline varied between an increase of 1.2% to an increase of 3.5%. The frequency of breaths in which $ETCO_2$% per breath was above 6.5% ranged between 0.7 and 7.7 breaths per minute, this was equivalent to 9% and 70% of all breaths reaching 6.5% or above across the 60-minute monitoring session.

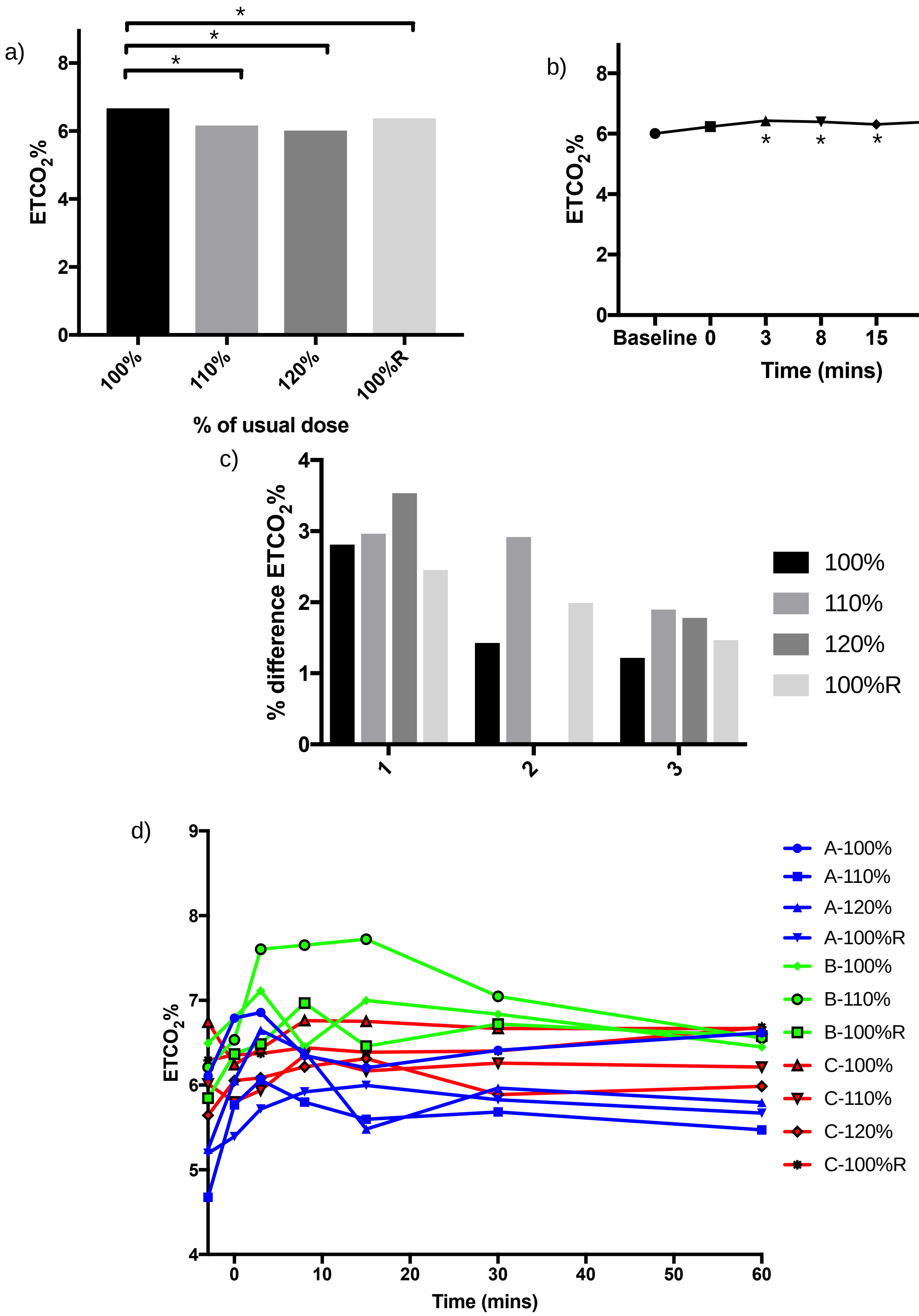


Figure 8-9a-d: $ETCO_2\%$ results.
a) median values for each session for all participants; b) one-minute averages of $ETCO_2\%$ for all participants at baseline (-3 minutes), 0, 3, 8, 15, 30 and 60 minutes after diamorphine administration; c) one-minute averages of $ETCO_2\%$ for each individual participant; d) % change from baseline for each participant and dose session. $ETCO_2\%$ = end-tidal carbon dioxide; 100%R = repeat 100% dose. Participant A = 1; Participant B = 2; Participant C = 3 *$p<0.05$

8.4.6.3 Transcutaneous carbon dioxide ($TcCO_2$)

Average $TcCO_2$ for all participants and all doses remained between 5.4kPa and 6.7kPa. Overall, there were significant differences between baseline and successive time points (Q=23, p=00008). There were significant increases in $TcCO_2$ at 8- (0.03), 15- (0.0005) and 30-minutes (0.003) post-dose compared to baseline (Figure 8-10a-c). There were significant differences between the 100% and 120% dose sessions (W=-105, p=0.0001), the 100% and repeated 100% (W= -231, p<0.0001), the 110% and 120% dose sessions (W=-77, p=0.01) and finally, in the 110% and the repeated 100% dose sessions (W=-179, p<0.0001).

There were no discernible differences between participants, although a slightly higher average was noted in Participant C. Participants A and C displayed breaths above 6.5kPa in almost all of the dose sessions, with the highest frequencies being noted in the 100% and 110% dose sessions. In terms of difference between baseline and peak $TcCO_2$ the greatest difference was observed in the 110% dose session with a median difference of 1.2kPa.

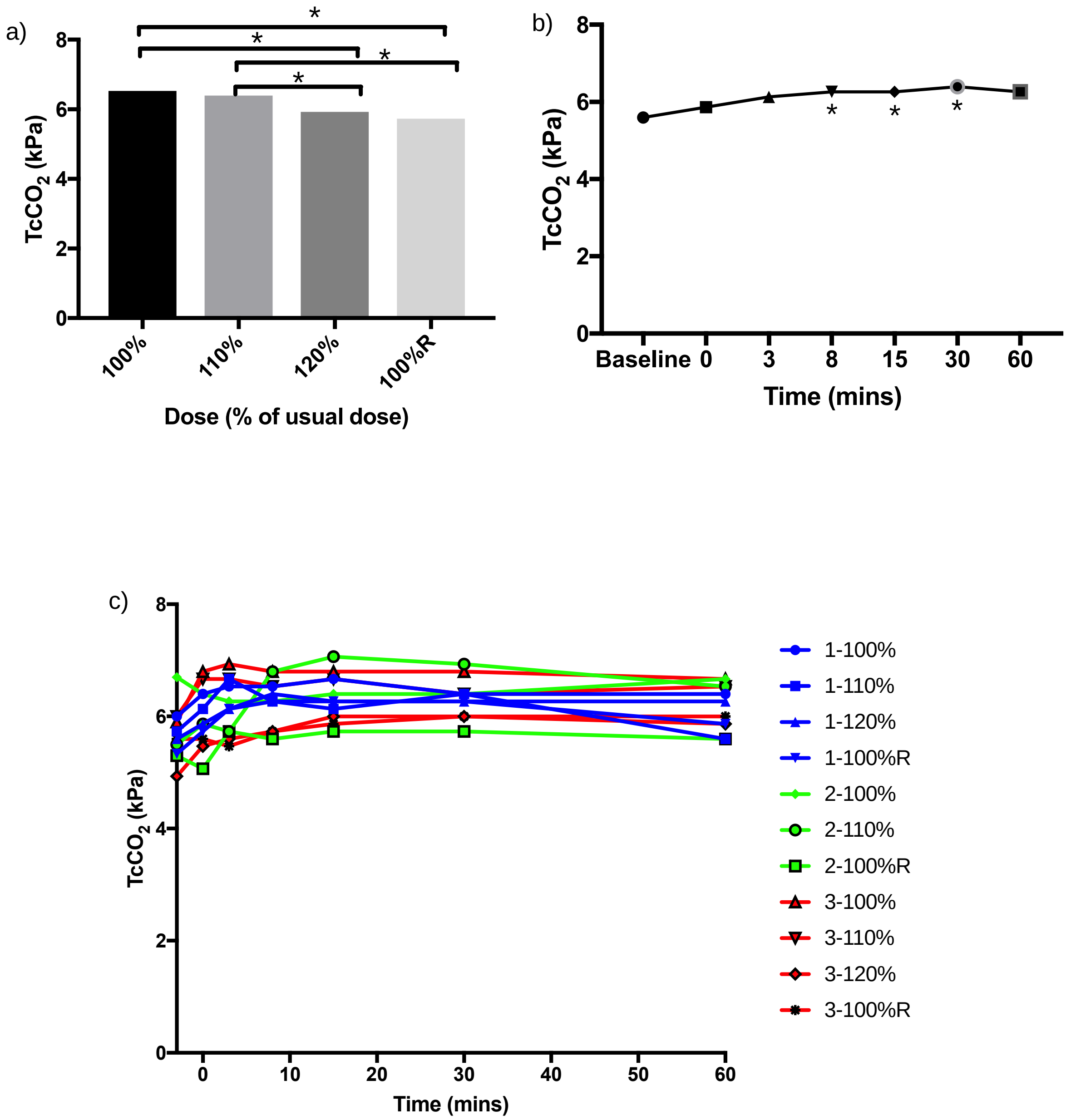


Figure 8-10a-c: TcCO$_2$ results.
a) median values for each session for all participants; b) one-minute averages of TcCO$_2$% for all participants at baseline (-3 minutes), 0, 3, 8, 15, 30 and 60 minutes after diamorphine administration; c) one-minute averages of TcCO$_2$% for each individual participant. TcCO$_2$% = transcutaneous carbon dioxide; 100%R = repeat 100% dose. Participant A = 1; Participant B = 2; Participant C = 3 *$p<0.05$

8.4.6.4 Neural Respiratory Drive Index (NRDI)

NRDI was varied between doses and participants. The highest level of NRDI was 166min^{-1} across all doses and participants (Figure 8-11a-d). Median values for the 100% dose sessions were 91.9 min^{-1} and 82.9 min^{-1} respectively and 96.2 min^{-1} and 88.5 min^{-1} for the 110% and 120% dose sessions, respectively. Overall, there were significant changes between baseline and successive time points (Q=19, p=0.04), with significant reductions in NRDI at 3- (p=0.03), 8- (p=0.02) and 15-minutes (p=0.002) post-dose. There were no significant differences in NRDI between doses (100%v110%=-39,p=0.9; 100%v120%=-13,p=0.7; 100%v100%R=-51,p=0.1).

Notable differences between participants were observed in the % change of NRDI from baseline. For each participant, there was generally less of a pronounced change from baseline with each study session, although a greater reduction from baseline was observed in the 110% dose session for participant A.

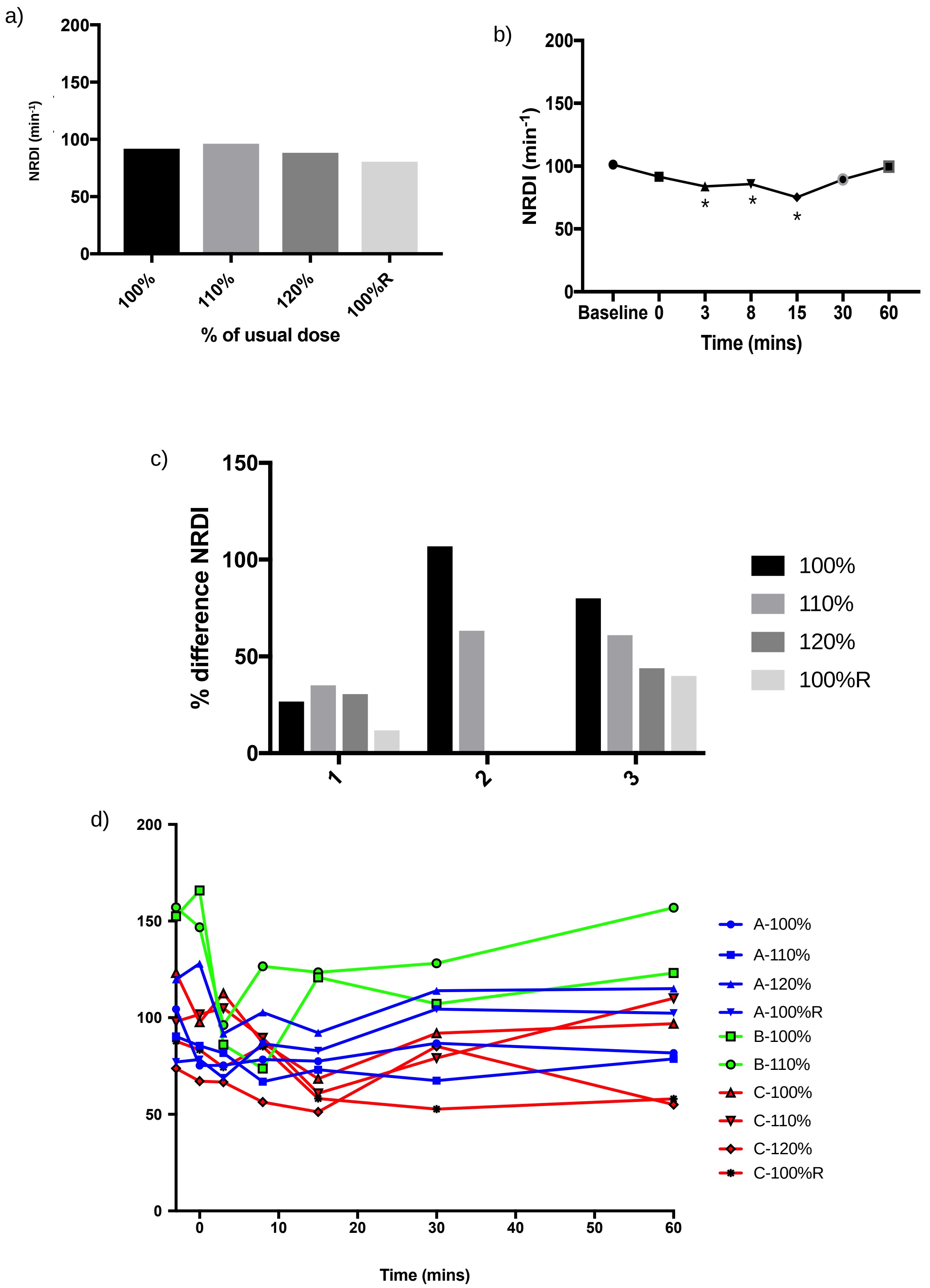


Figure 8-11a-d: NRDI results.
a) median values for each session for all participants; b) one-minute averages of NRDI for all participants at baseline (-3 minutes), 0, 3, 8, 15, 30 and 60 minutes after diamorphine administration; c) one-minute averages of NRDI for each individual participant; d) % change from baseline for each participant and dose session. NRDI = neural respiratory drive; 100%R = repeat 100% dose. Participant A = 1; Participant B = 2; Participant C = 3   *p<0.05

8.4.6.5 Respiratory rate and flow

Overall, respiratory rate was between 5.2 and 13.4 breaths/minute across all doses and participants. Overall, respiratory rate was significantly different from baseline to successive time points ($Q=23$, $p=0.0008$), with significantly lower rates at 3- ($p= 0.005$), 8- ($p<0.0001$) and 15-minutes ($p=0.007$) post-dose time points (Figures 8-12a-b and 8-13a). There were increases in breaths per minute between all of the dose sessions: 100% and 110% ($W=101$, $p=0.0004$), 100% and 120% ($W=77$, $p=0.01$), 110% and repeated 100% ($W=-119$, $p=0.04$) and 120% and repeated 100% ($W=-85$, $p=0.005$). Additionally, a similar pattern was seen within each participant, where increases in respiratory rate were observed in the higher dose sessions.

All participants experienced pauses of inspiratory flow in all dose sessions. The frequency of pauses (apnoea-hypopnea index, AHI) and % time spent with absence of flow across the 60-minute monitoring varied greatly across participants (Figure 8-14). The number of pauses ranged from 9 to 65 per session and lasted on average between 1.7 minutes (2.9% of total time) to 25.8 minutes (45.9% of total time).

The length of apnoeas ranged from 10 seconds to 56 seconds. Pauses were present throughout each dose session and sometimes occurred from baseline, prior to diamorphine administration, until the last minute of recording. Apnoeic episodes were present with subsequent increases in levels of end-tidal carbon dioxide and desaturation in peripheral oxygen readings (Figure 8-14).

With regard to tidal volume, overall, more varied changes occurred in tidal volume, with an initial decrease, and then increase in V_T from 100% to 110% and 120%, respectively (Figures 8-12c-d and 8-13b). None of the changes from baseline to successive time points for V_T were significant ($Q=8$, $p=0.2$). The median V_T across all doses and participants was 0.5L with a minimum of 0.2L, 0.2L, 0.1L and 0.1L being observed in the four sessions, respectively. There were no significant differences across the dose sessions (100%v110%=-71,p=0.2; 100%v120%=-15,p=0.7; 100%v100%R=-99,p=0.09).

Minute ventilation levels also somewhat varied across the doses (Figures 8-12e-f and 8-13c). Overall, there were significant differences between baseline and successive time points ($Q=17$, $p=0.01$). Specifically, there were significant decreases in minute ventilation between baseline and at 3- (p=0.005), 15- (p=0.01) and 30-minutes (p=0.02) post-dose. The median was 5.4L/min overall, with minimum levels reaching 1.5L/min, 1.3L/min, 1.6L/min and 1.2L/mins across the four a) ses, respectively. None of these changes were significant across the dose sessions (100%v110%=-25,p=0.7; 100%v120%=-3,p=0.9; 100%v100%R=-105,p=0.07).

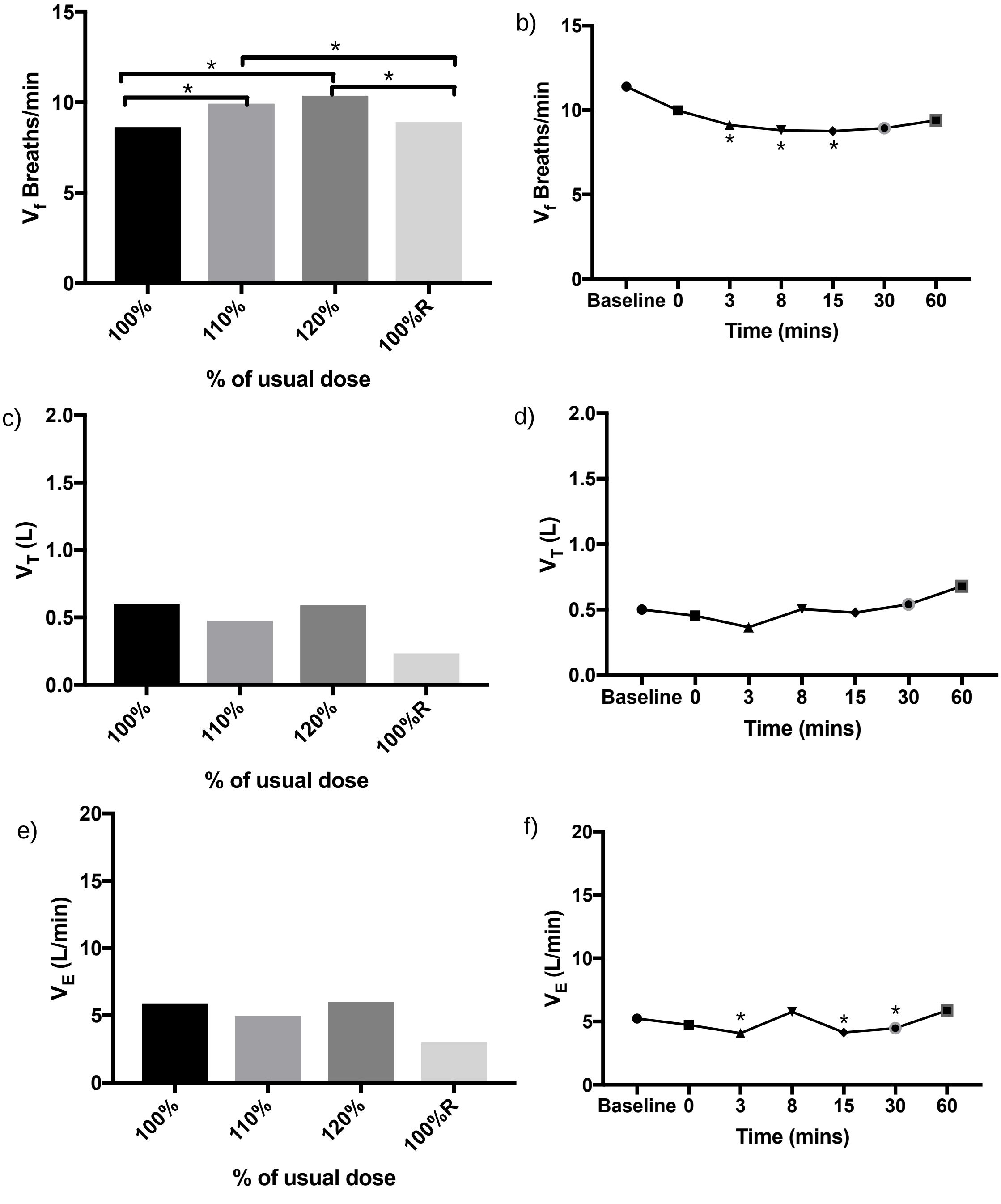


Figure 8-12a-f: Respiratory rate and flow results.
All graphs show median values across each dose session as well as one-minute averages at baseline (-3 minutes), 0, 3, 8, 15, 30 and 60 minutes after diamorphine administration for Vf, VT and V_E; a) Vf median values; b) Vf one-minute averages; c) VT median values; d) VT one-minute averages; e) V_E median values; f) V_E: one-minute averages. Vf= respiratory rate; VT= tidal volume; VE= minute ventilation; 100%R = repeat 100% dose. *p<0.05

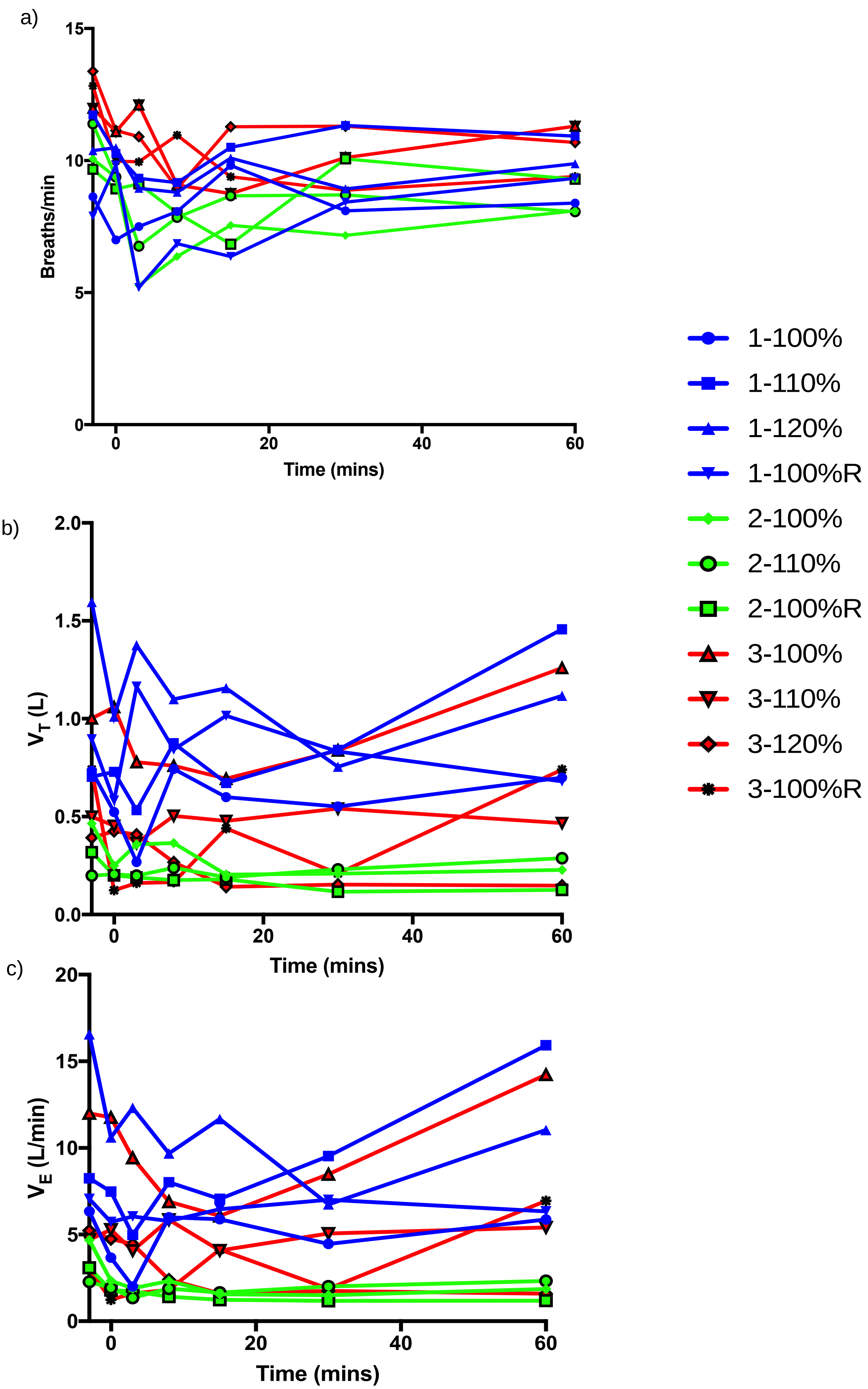


Figure 8-13: % change from baseline for each participant and dose session for a) Vf, b) VT and c) V_E.

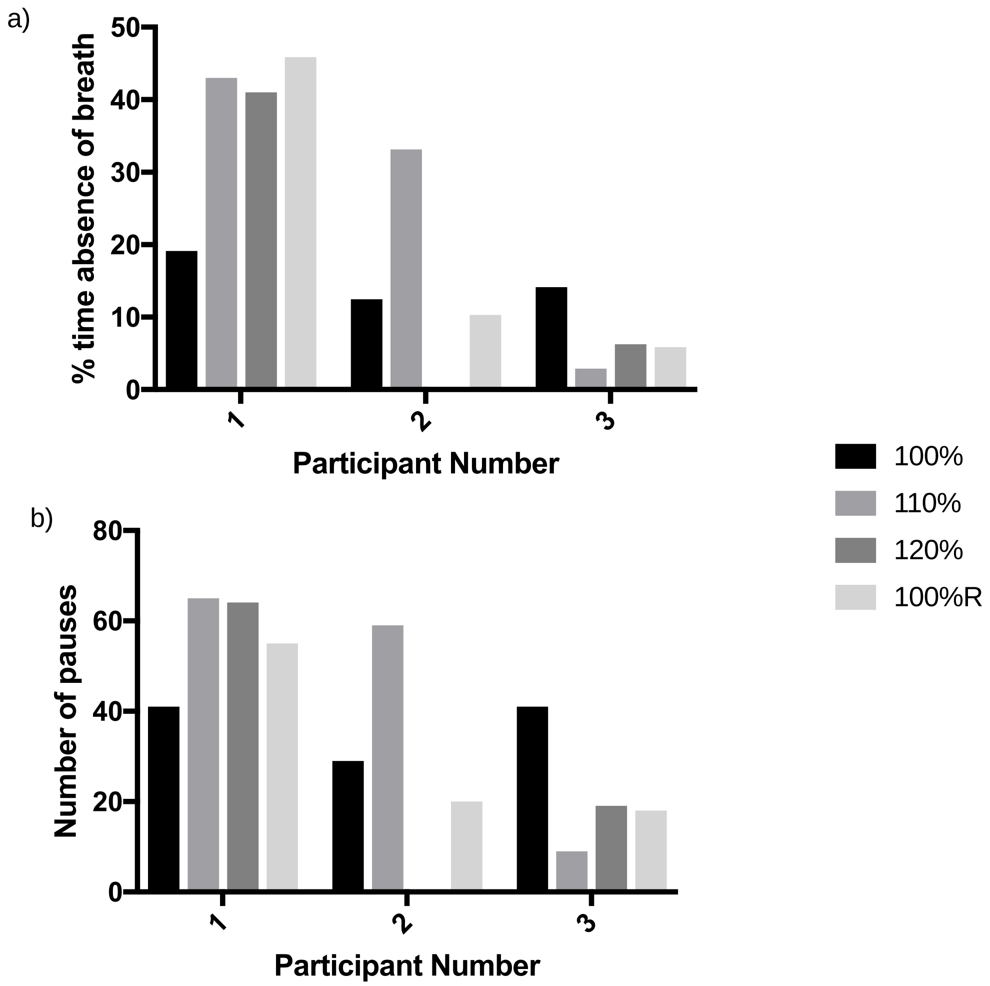


Figure 8-14a-b: Respiratory pauses.
a) frequency of apnoeic pauses of longer than 10secs; b) % time with absence of breath across 60 minutes. 100%R = repeat 100% dose. Participant A = 1; Participant B = 2; Participant C = 3 *p<0.05

8.4.7 Summary of Differences Between Baseline and Successive Time Points

Significant changes from baseline to successive time points were seen in SpO_2, $ETCO_2$, respiratory rate, V_E as well as NRDI. These changes were especially between the 3 minutes prior to administration (baseline) and 3-, 8- and 15-minutes post-drug administration. Some of the measures continued to show significant difference from baseline at 30 minutes post-dose (V_E and $ETCO_2$). Almost all measures recovered back to figures that were seen in baseline, with the exception of $ETCO_2$%. There were non-significant changes from baseline to successive time points in VT. These values alternated from baseline across the 60 minutes of monitoring and did not show a substantial increase or decrease overall.

8.4.8 Summary of Differences Between Doses

SpO_2, NRDI, V_E and VT showed some changes between doses but there were no significant differences between doses for these measures, including between the two 100% dose sessions. Three of the measures showed some significant differences between some of the doses. $ETCO_2$% was significantly lower in the 110%, 120% and repeated 100% dose sessions compared to the first 100% dose session. Respiratory rate was significantly higher between the higher dose sessions compared to the both 100% dose sessions. $TcCO_2$ was significantly lower in the higher doses and the repeated 100% dose compared to the first 100% dose session.

Individually, Participant A showed significant changes across doses for all measures except SpO_2%. Participant B showed significantly lower levels of VT between the two usual doses and significantly higher levels of $TcCO_2$ between 110% and repeat 100% dose session, but no other significant changes. Participant C showed significantly lower levels of $ETCO_2$, NRDI and $TcCO_2$ in the higher dose sessions compared to usual dose.

8.4.9 Secondary Outcomes: Subjective Effects and Observer Ratings (Aim 2)

Aim 2: To investigate effect of variations in heroin dose on subjective drug effect.

The second part of this chapter will focus on the various measures of subjective and observed drug effects. Each individual measure will be described separately. Measures of drug effect, drug liking and drug sedation as well as observer rating of intoxication were assessed at the seven successive time points post-administration. All were measured on a 100mm scale.

8.4.9.1 Pupil Size

Pupil size varied between 3mm and 1.5mm (Figure 8-15). Overall, across all participants, pupil size was significantly different from baseline to successive time points (Q=20.5, p=0.002). Pupil size was significantly lower in the 3- (p=0.04) and 8-minute (p=0.02) time points post-dose compared to baseline. Between doses, there was a significant decrease between both 100% and 110% (W=-94, p=0.005) and 100% and 120% (W=-28, p=0.02) dose as well between the 100% dose sessions (W=-131, p=0.0009). Individually, there was minimal variation in pupil size.

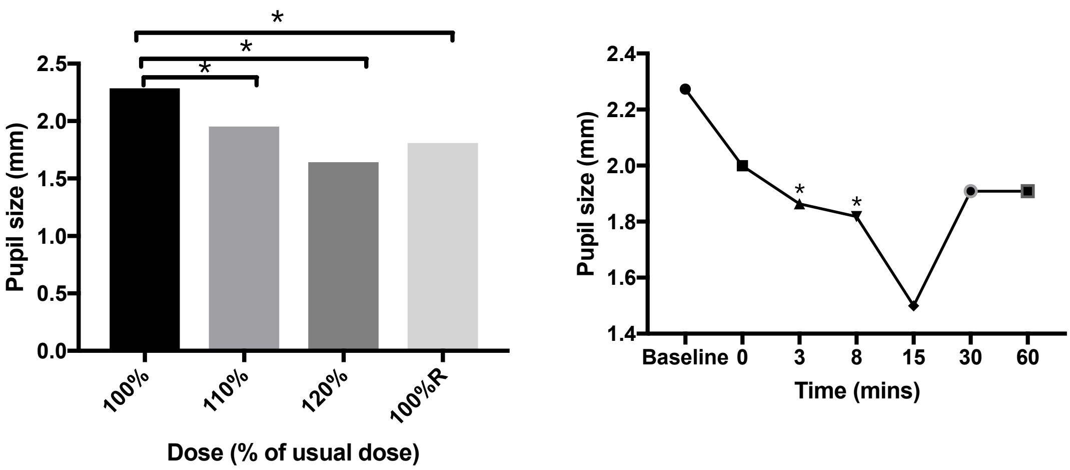


Figure 8-15: Pupil size.
Left: median values for each session for all participants for pupil size; right: one-minute averages of pupil size for all participants at baseline (-3 minutes), 0, 3, 8, 15, 30 and 60 minutes after diamorphine administration. 100%R = repeat 100% dose. *p<0.05

8.4.9.2 Drug Effects

Overall, across all participants, the subjective drug effects ranged from 0 to 92mm (Figure 8-16). Overall, there were significant differences from baseline to successive time points (Q=37, p=0.0001) with significant increased responses being observed at all successive time points (3- (p=0.008, 8- (p=0.001), 15- (p<0.0001), 30- (p<0.0001), 60-minutes (p=0.0009)). However, there were no differences between any of the doses (100%v110%=21, p=0.7; 100%v120%=24, p=0.4; 100%v100%R=-1,p=0.9). There was an average of 29mm, 34mm, 31mm and 44mm in each dose session, respectively.

Participant A experienced the highest level of drug effect in the 110% and then subsequently with the 120%. The lowest experience was in the first 100% dose session. When asked which session was thought to be highest dose increase, the response was 110%. Participant C experienced the lowest level of drug effect of the three cases and the highest level was in the 110%.

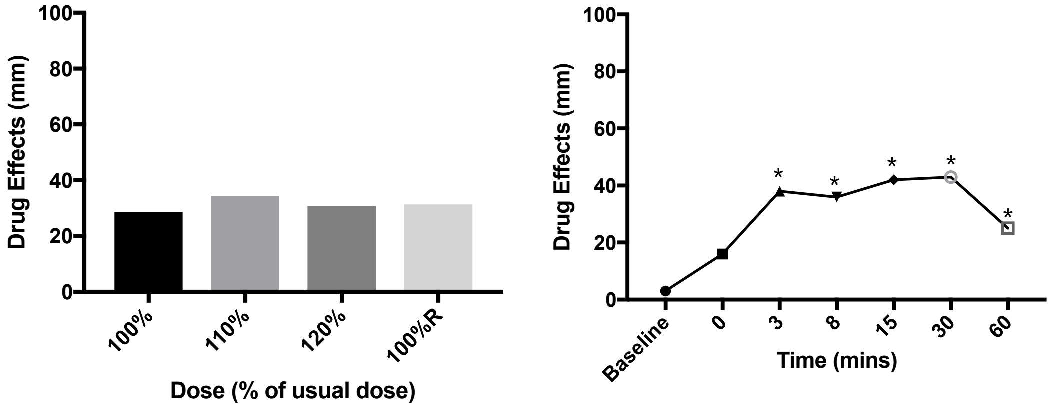


Figure 8-16: Drug effects.
Left: median values for each session for all participants for subjective drug effects; right: one-minute averages of subjective drug effects for all participants at baseline (-3 minutes), 0, 3, 8, 15, 30 and 60 minutes after diamorphine administration. 100%R = repeat 100% dose. *p<0.05

8.4.9.3 Drug Liking

This measure ranged from 0mm to 96mm with an average in each dose of 61mm, 60mm, 62mm and 87mm, respectively (Figure 8-17). Friedman's test showed overall non-significant differences between time points but a significant difference between baseline and 30-minutes (Q= p=0.008) was observed. There were no significantly different results (100%v110%=-30, p=0.6; 100%v120%=31,p=0.3), except for between the two 100% dose sessions (W=-114,p=0.04).

Individually, Participant A showed the highest level of drug liking amongst all participants and experienced the highest level in the repeated 100% dose session. Participants 2 and 3 showed similar levels of drug liking around the 40mm to 60mm level on average.

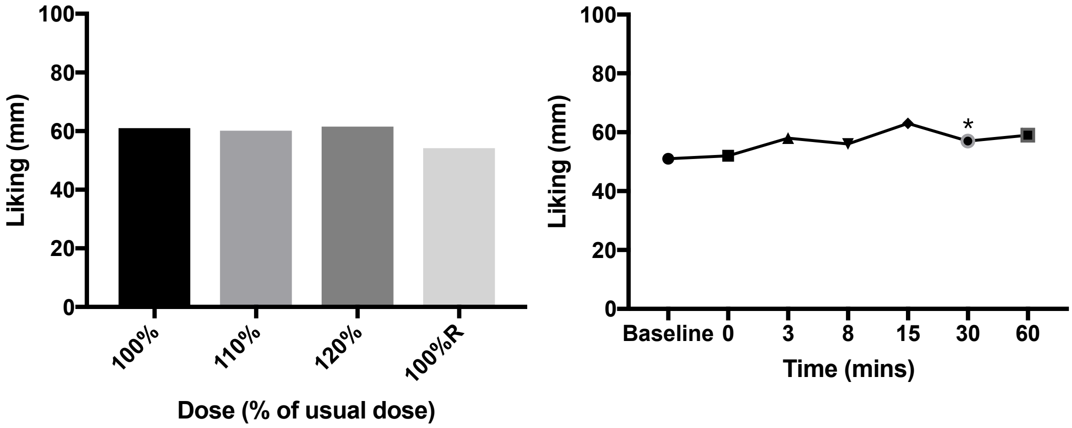


Figure 8-17: Drug liking.
Left: median values for each session for all participants for subjective drug liking; right: one-minute averages of subjective drug liking for all participants at baseline (-3 minutes), 0, 3, 8, 15, 30 and 60 minutes after diamorphine administration. 100%R = repeat 100% dose. *p<0.05

8.4.9.4 Drug Sedation

This measure ranged from 0mm to 91mm and an average across each dose session was observed as: 32mm, 42mm, 29mm and 47mm, respectively (Figure 8-18). Overall, significant changes occurred over time points, post-dose (Q=31, p<0.0001). A significantly greater level of sedation was experienced at all time points post-dose (p=0.03, p=0.002, p<0.0001, p<0.0001 and p=0.003, respectively). Increased levels of sedation were experienced in the 110% and repeat 100% dose sessions, significant differences were observed between 110% and 120% doses only (W=-71, p=0.02), the rest were not significant (100%+110%=83,p=0.2; 100%+120%=26,p=0.3; 100%+100%R=39,p=0.5).

Individually, Participant A felt the highest level of sedation and showed a maximum of 90-91mm within the three latter dose sessions (110% to repeat 100%). Participant B experienced the highest level of sedation in the first 100% dose session and Participant C experienced the lowest level of sedation with a average of between 9mm to 13mm across all doses.

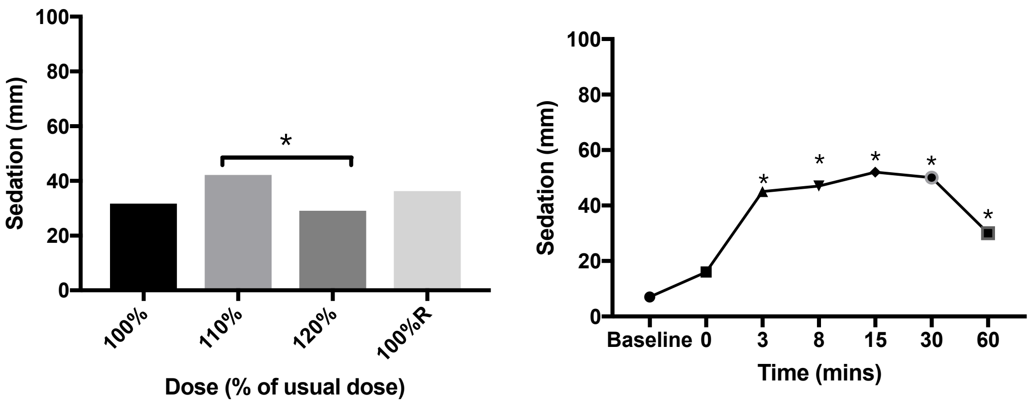
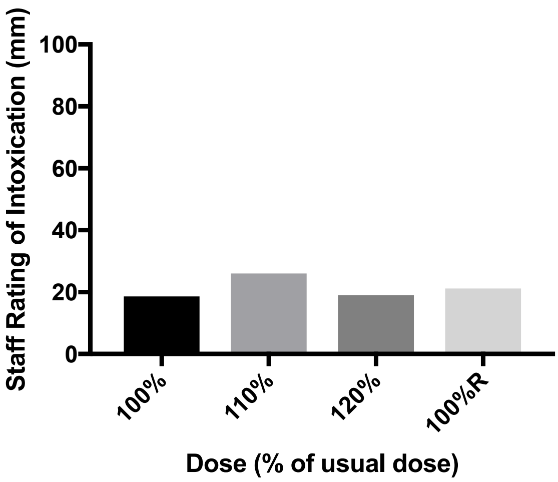


Figure 8-18: Drug sedation.
Left: median values for each session for all participants for subjective drug sedation; right: one-minute averages of subjective drug sedation for all participants at baseline (-3 minutes), 0, 3, 8, 15, 30 and 60 minutes after diamorphine administration. 100%R = repeat 100% dose. *p<0.05

8.4.9.5 Staff Rating of Intoxication

This measure ranged from 0mm to 96mm and the average rating for each dose session was 19mm, 26mm, 19mm and 44mm, respectively (Figure 8-19). Overall, significant differences were observed from baseline to successive time points (Q=38, $p<0.0001$). A greater level of intoxication was observed at 8- ($p=0.0003$), 15- ($p<0.0001$), 30- ($p<0.0001$) and 60-minutes ($p=0.003$) post-dose compared to baseline. Increased levels of sedation were experienced in the 110% and repeat 100% dose sessions but these were not significant.

Individually, ratings on the level of intoxication were greatly varied. Participant A had an observed highest level of intoxication in the repeat 100% dose session, followed by the 110% dose session. On average, the first 100% dose session was rated the lowest (6mm). Participant B showed the highest intoxication level at 110% dose session of 67mm but on average, the higher value was the first 100% dose session. Participant C displayed the lowest rating of intoxication at between 10-15mm on average.



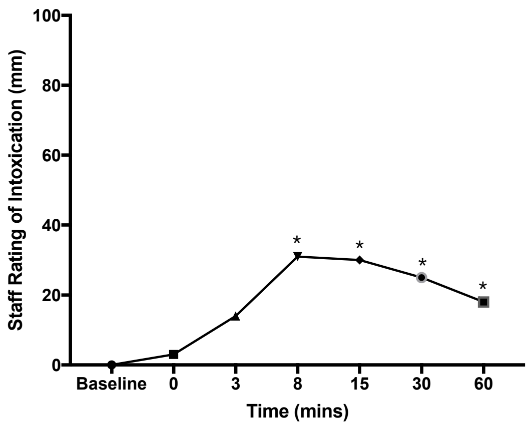


Figure 8-19: Staff rating of intoxication.
Left: median values for each session for all participants for staff rating of intoxication right: one-minute averages of staff rating of intoxication for all participants at baseline (-3 minutes), 0, 3, 8, 15, 30 and 60 minutes after diamorphine administration. 100%R = repeat 100% dose. *$p<0.05$

8.4.9.6 Glasgow Coma Scale/Level of Consciousness

There were little to no changes in the GCS scores across all participants and doses (Figure 8-20). There were 3 time points in one dose session that showed a slightly lower score indicating less consciousness. This was in 3-, 8- and 15-minutes post-administration in the 100% dose session for Participant A as well as in the 110% dose session at the 3-minute time point for Participant B.

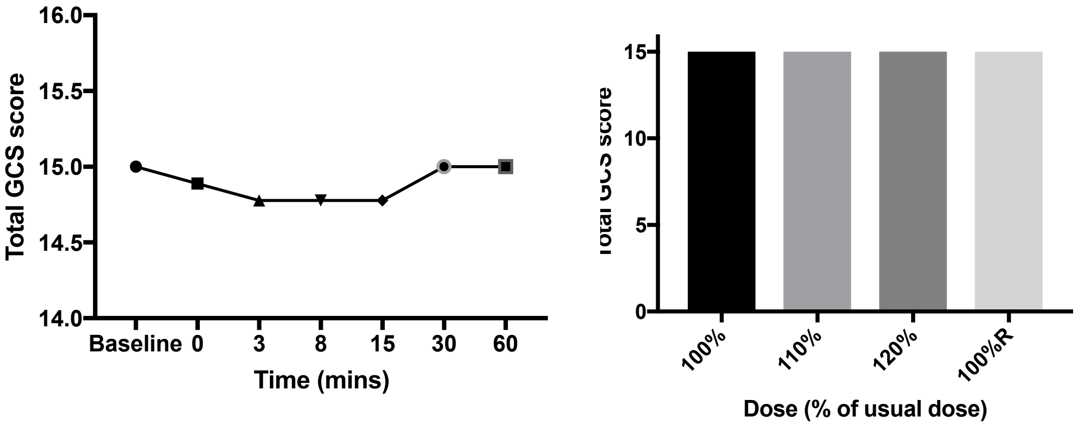


Figure 8-20: Level of consciousness:
Left: median values for each session for all participants for level of consciousness; right: one-minute averages of level of consciousness for all participants at baseline (-3 minutes), 0, 3, 8, 15, 30 and 60 minutes after diamorphine administration. 100%R = repeat 100% dose. *p<0.05

8.5 Discussion

8.5.1 Summary of Principal Findings

Overall, a severe respiratory depressant response was observed in all participants across all doses. However, a varied response was seen to increases in diamorphine dose amongst this population of long-term diamorphine-maintained users. Except for pupil size, observed and subjective ratings of drug effect and experience did not vary greatly between doses.

Individually, there were varied changes of respiratory measures between doses. Interestingly, there were significantly higher levels of the ventilatory parameters and NRDI in the higher doses for Participant A and higher levels of capnography parameters and NRDI for Participant C. Participant B, who showed severe overall responses, did not show significant differences between doses except in $TcCO_2$ (a higher level in the 110% dose session) and VT (lower level in the repeated 100% dose session). SpO_2% did not significantly change between doses for any of the participants.

8.5.2 Interpretation of Results

Generally, the results from baseline to successive time points post-drug administration were as expected across all the respiratory depression measures. There were significant changes at time points that are correlate with the peak effect of the drug (eMC, 2013; Klous, Van den Brink, Van Ree, & Beijnen, 2005). For example, there were more pronounced changes in the initial first few minutes for NRDI, SpO_2%, $ETCO_2$% and respiratory rate. $TcCO_2$ is a delayed measure and thus the significant changes occurred after the 15-minute time point.

What is of note is the variation in responses between doses across the three participants. There are two specific points in relation to this: firstly, it must be prefaced that the numbers are too small to form any definitive conclusions and the discussion on these data must only be considered as an opportunity to reflect on preliminary findings. Secondly, whilst some of the observations are unexpected, the observations are not unusual. The three cases presented in this chapter are all male, long-term injecting heroin users with similar use history and patterns; the differing aspects of these cases are related to daily use, prescribed dose and concomitant drug use. Thus, arguably, there are three different cases here that deserve discussion separately.

All participants showed a dose response effect in % difference from baseline to peak $ETCO_2$% which was interestingly the opposite effect seen in the NRDI % difference from baseline to nadir. Frequency of apnoeic pauses showed a dose-response effect in two of the participants. Across the three participants, NRDI and respiratory rate did not reduce with increasing doses of diamorphine. Oxygen saturation and carbon dioxide reduced and increased, respectively, with increasing doses of diamorphine proportionally but these were not significant. Participant B showed major impairment with an increasing 10% dose of diamorphine. With respect to drug effects and experience, very few measures showed notable changes. Pupil size showed a significant dose response effect, with decreasing diameter at higher dose levels, which has also been shown in the previous acute heroin study. There was a lower level of drug sedation experienced in the 120% dose session compared to the 110%, but not between 100% and 110%, which does not follow a dose response effect.

From these data, it could be suggested that it is more likely that overdose is more affected by individual variability rather than one or two overarching factors. The rest of this section will discuss the individual cases and subsequently wider implications of the data.

8.5.3 Case 1, Participant A

This participant administered 30mg as the usual dose, intravenously, for the study. Considerable respiratory depression was seen across all sessions but no significant differences occurred between usual and increased diamorphine doses. There was no indication that a 10% or 20% increase produced any more impact on this participant than their normal dose. In two sessions, baseline levels were also disturbed, i.e. in the two 100% dose sessions, there were apnoeic pauses, high levels of both $ETCO_2$ and $TcCO_2$ in the time prior to drug administration. It would appear that there is cause for concern more generally with this particular case and there could be an effect of the morphine sulphate which, in this case, was a long-acting form and was taken three to four hours prior to the study session, at each study session. Nevertheless, the scheduling of prescribed medications did not differ from his normal routine as noted through in-depth medical history and discussion with participant on each study day.

An interesting further analysis for this type of case would be an examination of the situation at different points in the addiction treatment. Fortunately, it is possible to compare the results for this participant from this study with the previous study on heroin overdose by my supervisors (5 years previously) as the same participant took part in both studies. From direct comparison, we observe that there were more pronounced effects seen in the previous dose for this participant where 100mg diamorphine was self-administered (IV) and the same physiological measures were recorded, with the exception of $TcCO_2$. For all measures, baseline values were more severe with the higher dose. It is somewhat expected that a higher dose would cause more severe respiratory depressant responses, but this creates further questions such as why would this occur if he is titrated to this particular dose? Also, why would there be less of an effect with a lower dose when the tolerance is high and the patient is stable? It could also be asked whether, if a 67% reduction in daily dose produces less pronounced effects, should it then be further encouraged that patients taper their dosing? On the other hand, it is also the case that this particular participant showed pronounced effects across every single dose session, and thus, clearly is affected by the respiratory depressant effects of opioids whether on a high or low dose, or a proportionally higher or lower dose injection. More detailed discussion of dose optimisation is discussed further on in this chapter.

8.5.4 Case 2, Participant B

This participant's usual dose was 100mg IV for the study and administered by the study doctor. There were considerable changes from baseline to successive time points as well as between the doses. Although overall, there was no statistically significant difference between the doses for Participant B, physiological measures did appear more severe compared to the other two participants. Additionally, a 10% increase affected his responses quite considerably and it was decided by the study team that it was not safe to proceed to the next dose increment of 20%. Figure 8-3 highlights the different observed responses to 100% and 110% doses.

The response observed in Participant B corresponds with the pharmacological hypothesis that an increase in dose leads to an increase in physiological responses and a more severe respiratory depressant effect. There are two points of consideration in relation to this. Firstly, the dose-sensitive effect may be related to the fact that his usual/habitual route of administration is intramuscular rather than intravenous, as tested in this study. Thus, an intravenous dose could be providing him with a more intense dose effect. However, if this were the case, we would expect there to be a severe response in the 100% dose sessions. It would be difficult to extrapolate this any further until there was further examination into the impact of route. For example, would he be expected to show similar responses whilst using IM? It would seem logical to hypothesise that there would be a less severe response with IM for this particular participant. Secondly, the dose-sensitivity could also be related to the extra 10% increase, this being equivalent to an extra 10mg diamorphine. The difference in response is considerably different, and this raises the question that if users slightly alter their doses of diamorphine in this way, how frequently do users reach this critical point and how close are users to death?

8.5.5 Case 3, Participant C

This was an intramuscular user administering a usual dose of 200mg diamorphine IM. There were no prominent differences between doses, but it must be noted that a level of respiratory depression was still reached. For example, his level of carbon dioxide was consistently over the 6.5% threshold. This indicates that alveolar ventilation is insufficient to maintain arterial carbon dioxide within the normal range. High levels of carbon dioxide do commonly occur with opioid use (Lehmann, Neubauer, Daub, & Kalff, 1983), however, combined with the commonly observed overlap with lung disease, this creates further problems for the user (Jolley et al., 2015b) (see Chapter 5 on overlap between heroin addiction and lung disease). The brief assessment of lung disease at the screening for this study shows that this particular participant also had underlying lung disease. Additionally, there appeared to be changes from baseline to peak or nadir effect for each of the measures that were comparable to the other two participants. Overall, this participant also reached similar respiratory depression criteria, and in some cases the frequency of these were higher than the other two participants, e.g. the frequency of respiratory pauses in the 100% dose session (41 pauses). Thus, although there appears to be an overall less severe respiratory depressant effect with intramuscular administration compared to the IV users, there was still a level of respiratory depression, and although, there was a more delayed responses and less intense initial post-dose effect, the duration of effect persisted until the end of the study session.

Interestingly, this participant’s level of drive became less severe with each session. The question of whether this is related to environmental factors must be raised. There is further discussion on this specific topic of environmental factors contributing to opioid overdose vulnerability further on in this chapter.

8.5.6 Secondary Outcomes: Subjective & Observer Ratings

All subjective and observer ratings increased from baseline to successive time points and there was variation between participants in how sensitive they were to dose changes.

Pupil size decreased significantly with each dose session and also, from baseline to successive time point in each session. As described in the previous chapter pupil size is a common measure of opioid effect as well as injury to the central nervous system. Contraction of the circular muscles that constrict the pupil response to light causes smaller pupil diameter, and a decreased, or pinpoint pupil, is commonly present in combination with decreased level of consciousness and respiratory depression. The findings here are also consistent with the previous study on acute heroin effects where pupil size was the only measure to show any difference between the two injecting routes of administration. It is also interesting and fits the pharmacological hypothesis that the pupil diameter significantly reduced with each increase in dose.

However, examining pupil size individually shows a different picture. It appears that only one participant showed variation between the doses, therefore, it is difficult to conclude whether this measure reliably demonstrated a dose response effect. Furthermore, the pupil size in the final (repeated 100% dose) was significantly lower than the first 100% dose session. This indicates a potential influence of environmental factors. This will be discussed in further detail later on in this chapter.

Overall, a greater level of drug sedation and drug effect was experienced in the 110% dose session and even greater in the repeated 100% dose session. Individually, these experiences varied even further. A similar pattern was observed in the staff rating of intoxication which appeared to show an increase in the 110% dose session compared to baseline but the greatest increase was in the repeat 100% dose session. A greater level of drug liking was experienced in the repeated 100% dose session which was an unexpected finding. It is thought that the drug liking experience increases as the dose increases. This suggests that perhaps again, environmental factors might have a role to play in the effects being observed.

8.5.7 Limitations

There are two main weaknesses of the findings and conclusions reported in this chapter. Firstly, it is difficult to draw conclusions based on small the number of participants presented in this chapter. Due to the unexpected obstacles, the data presented in this chapter were limited to a case presentation for the purposes of submitting the thesis.

Secondly, pharmacokinetics was not conducted on the participants. In the initial drafting of the study protocol, taking blood samples from this population were deemed unsuitable. This was driven by the initial consultations with service users, as well as the fact that peripheral venous access is known to be difficult amongst long-term injecting drug users. In fact, there were issues related to peripheral venous access during assessment of whether IV would be suitable in amongst all participants who screened for the study.

8.5.8 Strengths

This is a greatly in-depth study that has been able to take a dwindling number of patients from a community of users who often feel insecure about their treatment to conduct crucial investigations into the physiological and subjective responses of increased doses of diamorphine. The ability to investigate critical questions of risk factors of heroin overdose in a reliable, well-designed study has provided a strong opportunity to elucidate some of the long-held questions in the field. Furthermore, the ability to capture as realistic scenario as possible, given the considerable number of influential factors, is a great strength of the study. From a physiological perspective, the findings in this study were also congruent. There were low levels of minute ventilation and increasing levels of end-tidal carbon dioxide, post-dose. These are expected physiological findings post-opioid dose.

8.5.9 Significance of Apnoeic Episodes

There were some observations in this study that were unexpected or that raised further questions and encouraged consideration. Throughout each study session, one of the most striking phenomena was the length of pauses observed in every study session. Whilst our safety guidelines were clear that a 20 seconds apnoea was a criterion that could result in an intervention (with a cascade level from least intrusive to most intrusive), it was most surprising that often the participants during these, sometimes lengthy, apnoeic episodes were not symptomatic or visibly disturbed in any way. Further, in some sessions these pauses and patterns remained evident for the length of the study session of 60 minutes (see 55 minutes post-dose in Figure 8-4). This was unexpected as the half-life of diamorphine is around 2-3 minutes. The metabolite morphine does remain for longer around 3-4 hours, but the peak effects are usually at around 15 minutes (eMC, 2016) (slightly sooner for intravenous).

Discussions were held with respiratory physiology and sleep medicine colleagues in relation to the data in this chapter. Apnoeic episodes and the pattern of flow breathing were a frequent point of discussion. In Sleep Medicine, there is a clear typology of breathing patterns that are centred on apnoeic pauses and the size of inspiratory breaths. Generally, it is considered that any pause in breathing of over 10 seconds that is also combined with hypoxaemia is considered dangerous and abnormal. In Sleep Medicine, this particular characteristic is considered a crucial feature of sleep apnoea (U. P. S. T. Force, 2017; Jayaraj, Mohan, & Kanagasabai, 2017). Obstructive Sleep Apnoea (OSA) and Central Sleep Apnoea (CSA) are the main forms of sleep apnoea, with CSA being more prevalent over OSA among users of opioids (Correa et al., 2015; Fahim & Johnson, 2012; Farney, Walker, Cloward, & Rhondeau, 2003; Teichtahl & Wang, 2007; D. Wang et al., 2005). OSA does still occur among people using opioids (between 8%-10% (Van Ryswyk & Antic, 2016)) but the mechanisms are not fully understood and it is thought to be related to the opioid-induced reductions in airway muscle activation (Hajiha, DuBord, Liu, & Horner, 2009). Further, it is thought that untreated sleep apnoea where patients stop breathing and which frequently occur during sleep ultimately leads to atrial fibrillation, cardiac arousal, stroke, brain or other vascular diseases or potentially death. It is understood that chronic use of opioids can also affect breathing during sleep, including non-apnoeic hypoxaemia, central and obstructive apnoeas and ataxic (irregular) breathing (Alattar & Scharf, 2009; Farney et al., 2003; Teichtahl & Wang, 2007; J. M. Walker et al., 2007). The onset and severity of respiratory depression and sleep-disordered breathing is highly affected by inter-individual variability and the factors underlying this susceptibility to overdose in certain individuals are poorly understood.

In the data presented here, some of the observed irregular patterns of breathing resemble 'sleep-disordered breathing' patterns. There are distinct patterns of breathing that fall under this umbrella and there are also suggestions that a distinct 'opioid-induced' type of sleep-disordered breathing exists and encompasses various abnormal patterns with questions over optimal treatment for this condition (Javaheri & Randerath, 2014; Randerath & George, 2012). In this study, breathing patterns could also be described as such due to the observed differing abnormal patterns (Figures 8-3 & 8-4). Similar varied patterns have been noted in studies exploring effects of opioid use: ataxic, Biot's, Cheyne-Stokes, as well as types that fall under OSA and CSA types of breathing have all been described in chronic opioid users (Farney et al., 2003; Mogri, Desai, Webster, Grant, & Mador, 2009; Van Ryswyk & Antic, 2016; Wang & Teichtahl, 2007; Webster, Choi, Desai, Webster, & Grant, 2008). Furthermore, opioid-induced sleep apnoea appears to be prevalent in between 30% and 90% of chronic opioid users (Fahim & Johnson, 2012). In a similar study of opioid administration in patients who use opioids for chronic pain, the patterns of breathing were seen as a mix of Biot's breathing and ataxic (Walker et al., 2007). Ataxic breathing is essentially a complete irregular pattern of breathing with irregular pauses/apnoeas. Biot's breathing is sometimes used interchangeably with ataxic breathing and it is described most effectively in the original research paper:

> This irregularity of the respiratory movements is not periodic, sometimes slow, sometimes rapid, sometimes superficial, sometimes deep, but without any constant relation of succession between the two types, with pauses following irregular intervals, preceded and often followed by a sigh more or less prolonged. (Biot, 1876)

Furthermore, some of the patterns observed in this study also appear to display 'waxing and waning' patterns characteristic of Cheyne-Stokes breathing. This particular condition can be seen most distinctively in Figure 8-4 in the 100% dose session of Participant A. Cheyne-Stokes respiration is characterised by gradual decrease in volume of inspiratory and expiratory breaths that results in temporary pause in breathing with a subsequent increase or faster rate of breathing. The pattern repeats every few seconds to 2 minutes and the oscillation resembles a crescendo-diminuendo pattern and is also associated with changes in levels of oxygen and carbon dioxide (Berssenbrugge, Dempsey, Iber, Skatrud, & Wilson, 1983; N. S. Cherniack & Longobardo, 1973; Dowell et al., 1971; Guyton, Crowell, & Moore, 1956). This pattern is not consistently present in all of the cases.

There is clearly not a regular pattern of breathing occurring amongst all of the participants, post-opioid dose administration, but it can be stated that perhaps a distinct 'opioid-induced' type of CSA is occurring amongst these participants. However, whilst sleep-disordered breathing is somewhat beyond the scope of this thesis, the patterns of breathing observed in this study warrant further investigation and reflection.

8.5.10 The Effect of Repeat Dosing

As mentioned in Chapter 3, when discussing the role of the environment factors and tolerance in opioid overdose vulnerability, it is imperative to consider the significant work of Siegel and others. This work arose from the difficulty in understanding the increase in heroin deaths in the 1980s in Canada and reflected on Pavlovian conditioning principles and its relation to drug tolerance (Siegel, 1982, 1983). Many differing views were presented to explain the causes of these worrying trends at that time and many of the proposed causes of deaths centred on the similarly discussed causes today. These causes were threefold: some people may be dying from a true pharmacological overdose (Huber, 1974), others may be dying from doses that are not expected to be fatal and presumably in individuals that are tolerant to the opioid effect (Brecher, 1972; Reed, 1980) and finally, some may also be dying from a synergism between the opioid and other drugs or adulterants. It was therefore described that some deaths are: 'an idiosyncratic reaction to an intravenous injection of unspecified material(s) and probably not a true pharmacologic overdose of narcotics' (Cherubin, McCusker, Baden, Kavaler, & Amsel, 1972, p. 11). It is of note that this would be relevant to today's trends, both in the UK and globally.

Siegel's work reflected on animal study investigations into a model of tolerance with underlying Pavlovian conditioning principles (Siegel, 1983). The interpretation of tolerance by Siegel and others was not based on a physiological one, but rather based on the premise that the individual's experiences with the drug administration environment has as much of an important contribution to tolerance dependence as physiological and pharmacological factors. This was thought to be another potential cause of overdose death. There was some evidence that in some cases overdose may be as a result of a conditional failure of tolerance when the usual pre-drug cues do not accompany the usual pharmacological consequences (O'Brien et al., 1992b; Siegel, 1983, 1984).

In relation to data presented in this chapter, it is reasonable to ask whether there could be a different mechanism at play here. Could there also be a potential combination of physiological/pharmacological as well as psychological? Or, ultimately, is there just no reliable effect at all?

Participants in this study were asked at every visit whether the effects of the drug appeared to be affected by the foreign nature of a laboratory setting and were asked to compare their experiences to previous visits in the study. None of the participants felt that the overall experience differed greatly from their usual experience at home and it must be stated that these particular participants are more likely to be used to administering their diamorphine in a clinical, hospital setting than their street-using peers.

Furthermore, there are a considerable number of studies that might contribute to understanding the unpredictability of opioid overdose. In the case of opioid analgesia medication, it is understood that the tolerance of analgesic properties of opioids develops faster than tolerance to respiratory depressant effects. With long-term use, this delayed tolerance restricts the therapeutic window and potentially places patients at increased risk for respiratory depression (Boyer, 2012; Etches, 1994; Gal, DiFazio, & Moscicki, 1982; White & Irvine, 1999). Could a similar phenomenon be occurring with a tolerance to the maintenance effects?

8.5.11 Speed of Administration

During the diamorphine administration, it was possible to record the speed of injection. When self-administering, speed of injection was no more than six seconds and was only slightly increased in one case when it was administered by the study doctor (12 seconds). This increased speed of injection did not appear to diminish the respiratory depressant effects of the diamorphine, in fact the session with the longest administration was the one that saw the most pronounced effect in all of the study sessions. During the planning phase of the study, there was discussion of incorporating a time range for injection. It was initially thought that injecting over 1 or 2 minutes would be most suitable. The discussion was originally centred on nurse administration via cannula but as the study protocol developed, self-administration was preferred to resemble the accurate injecting situation and this timing of injection became 'self-administer the diamorphine in under 1 minute'. In practice, the speed of injection was much quicker.

It is not known whether a slower administration would have resulted in less severe responses, but we could logically assume that this might be the case. However, this would not be reflective of realistic using scenarios.

8.5.12 Implications for Clinicians and the Community

There are three main implications for clinicians. Firstly, a clinical investigation into whether this type of monitoring could actually reduce the risk of respiratory depression is required. Could intensive monitoring reduce risk of significant respiratory depression? Findings here and the previous heroin administration study show that there is need for careful physiological studies of the mechanisms and how and where these data can drive technology. These types of intricate, detailed physiological measurements are able to identify markers that could be used to identify 'at-risk' patients and potentially allow for an early detection of risk of opioid overdose. It is feasible that this type of testing could be conducted in patients before treatment and, in the future, even be used as a means of providing opioid users better information on which to choose their treatment. However, as mentioned in Chapter 5 these methods require further validation in larger scale, prospective studies.

Secondly, there is the issue of dose variability and titration. It should be made clear that there is no suggestion from this study that heroin maintenance medication should be reduced for the purposes of reducing risk of overdose. A careful balancing act is already involved in the process of dose optimisation, and the negative effects of opioids are very well-understood. The UK guidelines on clinical manage of drug misuse and dependence (The 'Orange Book') (DOH, 2017) state that the objective of dose optimisation is a complete cessation of heroin and other illicit opioid use. Additionally, better outcomes of cessation of all heroin use are usually observed at higher doses of opioid substitution drugs. It is generally recommended that average doses of methadone are between 60 and 120mg and buprenorphine between 12 and 16mg daily, with some requiring higher or lower than this range. Finally, guidelines state that patients need to be informed on what is likely to be most effective for them.

Taking these points into consideration, the data presented in this chapter and the data that may continue to arise from this study could be used to help further inform patients in the process of treatment optimisation. Further, there are potentially informative pieces of advice that could arise from this type of work. There are a potential four pieces of information that could be considered by the clinical and service user communities further. Firstly, should non-IV, i.e. IM and SC, be further encouraged for clients to move forward to? Secondly, underlying lung disease could be considered an important factor in increasing vulnerability overdose, and subsequently, opioids may be masking symptoms of breathlessness that may be experienced. Thirdly, and in relation to the previous point, having a respiratory infection, from a cold to a chest infection may also leave the user more vulnerable and it may be sensible to be aware of extra precautions. Fourthly, if in an informal using situation, how long should friends, relatives or peers wait if someone is not breathing? Additionally, should the response to the pause in breathing be a simple physical manoeuvre such as a nudge, or should there be a cascade of events, starting from verbal, then physical, then painful and then act upon the situation if there is no response to painful stimuli? The latter point is part of standard practice and training in relation to overdose prevention, but if clinical data are showing a more complex phenomenon, it is pertinent that this training and practice is more nuanced. Although it must be noted that these pieces of information are inconclusive thus far, this work does allow one to develop a stronger picture of how this could proceed.

Thirdly, another implication for clinicians is that respiratory depression occurred at all doses in this study. It is of note that the responses between the two 100% dose sessions were not identical, suggesting that the responses differ despite the same dose being administered. This could be related to environmental factors as highlighted previously, and it is an interesting phenomenon that has been observed in supervised injectable treatment clinics, as mentioned in the introduction of this chapter.

8.5.13 Public Health and Policy-Related Implications

There have been great efforts to address overdose deaths through public health and policy initiatives. By collaborating with other public bodies, the Office of National Statistics (ONS) annual report on deaths related drug poisoning in England and Wales (ONS, 2018), as well as the National Records of Scotland's publication (NRS (National Records of Scotland), 2018) on drug related deaths in Scotland contribute the predominant mortality trends within the UK. Within these reports, there is often crucial discussion of potential causes behind any changes to the numbers of deaths. Since the major upward trend of opioid-related deaths in the UK from 2012, the main reasons that were provided in these reports were based on the occurrence of a Heroin Drought (M. Harris et al., 2015) and subsequent increase in purity as being responsible for this increase. Essentially, the issue was connected to small fluctuations in the black market. However, as has been discussed in the introductory chapters and through the data presented in this chapter, the issue is clearly more complex. Previous literature has shown that it is uncertain whether small fluctuations in the market actually result in an increased risk of overdose (Darke, 2011b, 2014; Darke et al., 2010a; Darke & Farrell, 2014; Davidson et al., 2003; Degenhardt et al., 2011). However, the governmental reports have repeatedly communicated this reason as being the centre of increases in deaths, and this has been further promoted by media outlets. Although it appears that this argument has been diminishing (ONS, 2018), the issue with this delves deep into the political nature of addiction treatment. Does the issue of providing reasons that have little or no evidence potentially mask more complex and controversial factors that may be contributing to the increase in deaths in the UK? Moreover, it is certain that the year-on-year financial burden experienced by the National Health Service and subsequent cuts to addictions services since 2010 (Rhodes, 2018) do not help the situation further.

8.5.14 Future Research

I propose that there are three further routes of exploration from these data that I will highlight:

1) Further this study and gather more data: in combination with this, explore whether IV and IM actually do lead to differences in physiological and subjective effects within subjects. There is progression with this point, and an application to the ethics committee will be made in order to re-invite the same participants that have been examined thus far to undertake the same sessions but with administration of a different route of injection. This would lead to a strong within-subject design.

2) Explore genetic influences behind overdose vulnerability: there had been discussion of including a genetic component within the study presented here. Advice was sought from experts within the social genetics field and colleagues from the Addictions Department of King's College London including from Professor John Marsden. The proposed idea stands that the OPRM1 gene, which is related to mu-opioid receptor sensitivity where the respiratory depressive actions lie, may have some involvement in individual variability of drug metabolism (Befort et al., 2001; Chidambaran et al., 2015; Goldstein, 2001; Manini, Jacobs, Vlahov, & Hurd, 2013). This is thought to be related specifically to the polymorphism A118G. There is a great deal of literature on pain responses and alcohol consumption in the presence of this polymorphism (Bilbao et al., 2015; Ray & Hutchison, 2004; Sloan et al., 2018; Yu, Wen, Shen, & Zhang, 2018), but limited to no evidence on physiological responses in opioid overdose. However, there are still questions that need to be addressed, e.g. what is the mechanism with which this receptor polymorphism exerts the effect? Is this a phenotypic effect? The other limitation with this is related to effect size. The sample size for this study (n=12) would be considerably too small to see an effect within a genetic study. This would clearly not be feasible amongst diamorphine-maintained patients in the UK. There could be some scope to expand this type of study to other opioid prescribed patients, or to street heroin users but this would be a separate exploration.

3) Alongside this work to further understand the physiology, there is significant scope for incorporating laboratory-based measures into wearable 'smart' technology. There is some development with this type of investigation and is discussed in the final chapter. As this thesis is being written, a plan to implement an exploration into wearable measures into the current study is being conducted.

Conclusions

A dose-incremental, single-blind, within-subject study into the effect of incremental doses of diamorphine on physiological and psychological measures in tolerant users was conducted. In-depth analysis on three participants as part of a case series presentation in this chapter aimed to demonstrate the interim results of this ongoing clinical experimental study. Primary outcomes were based on physiological measures of oxygen saturation, carbon dioxide, respiratory drive and results were varied across all doses and participants. In two of the participants, there appeared to be some effect of dose increases but in-depth analyses showed that one of these individuals had disturbed baseline measures prior to drug administration. The third participant administered intramuscularly and results did appear to be less severe, although still showed some signs of respiratory depression.

Ultimately, the data presented and observed thus far show an inter-individual variability that is not predictable. This is in accordance with available literature on the seemingly erratic nature of fatal overdose cases. Overall, it would appear that long-term heroin users are not necessarily tolerant to the respiratory depressant effects of opioids but crucially, continuation of the investigation is required along with further investigation into different routes and practical and wearable technologies.

9 Discussion

Table of Contents

9.1 Summary of Principal Findings and Contribution to the Addictions Field.

Chapter 1: This opening chapter describes the overview of global and national opioid-related deaths and considers the reasons behind the increase in the UK death figures over the last six years, particularly focussing on purity. It also examines why it is difficult to interpret global drug-related deaths (DRDs) data and reflects on the opioid crisis in the USA.

Chapter 2: This chapter examines the history of heroin use and heroin addiction treatment in the UK and the reasons why the experimental study of heroin effects is possible in the UK. Prior to the 1970s, the mainstay treatment for heroin addiction in the UK was diamorphine prescribing. It is unlikely that a similar structure that existed prior to the 1970s in the UK will exist again and hence it is vital to learn as much as possible from the retrospective examination of data from this earlier era and to consider their relevance to the situation of today.

Chapter 3: This chapter describes the distinct pharmacological and physiological effects of heroin and other opioids and focusses on the underpinnings of respiratory depression and respiratory function in long-term opioid users. Opioids are a particularly interesting group of drugs that have been used for centuries for their pain-relieving, sedative, anti-anxiety and cough suppressant effects. However, they also possess a side effect which has been the great focus in pharmaceutical development over many decades: respiratory depression - a dangerous reduction in breathing. The severity of respiratory depressant effects varies between opioids, but there is no opioid agonist that does not have this effect. This chapter also describes physiological mechanisms in three distinct cases: in an opioid overdose, in healthy individuals, and amongst those with underlying chronic lung disease. Finally, this chapter provides a rationale for each physiological measure of respiratory depression used in this thesis.

Chapter 4: this chapter highlights the various physiological and respiratory measures, criteria, assessments and techniques that were involved in the studies related to this thesis and were used to measure the level of respiratory depression. The chapter also describes the subjective measures of drug effect and breathlessness. Without a standard measure of respiratory depression, there are various physiological measures and techniques that are required to be incorporated. It is possible to detect respiratory depression in individuals using reliable and accurate physiological measures.

Chapter 5: This chapter is devoted to an observational study examining respiratory function among clients of a drug treatment centre. Everyday respiratory depression exists within healthy drug users as well as those with lung disease. Compared to controls, a significant respiratory system 'burden' was seen. Being able to elicit these data by means of a simplified, practical method shows that it can be taken further into a clinical setting or inform further technological developments to improve early detection of opioid overdose. Furthermore, the results also show that certain personal, behavioural, drug treatment and use factors are related to chronic respiratory depression. Finally, the results also show that the neural respiratory drive to breathe appears to be significantly lower in opioid users with underlying lung disease compared to controls with lung disease.

Chapter 6: This chapter re-examines data from a previous study on acute heroin effects (Jolley et al., 2015). Results from the data presented in this chapter suggest a varied physiological and subjective response to differing routes of heroin administration. It is not clear from these data whether intravenous (IV) does actually have a more pronounced physiological effect compared to intramuscular (IM) administration. However, subjective effect and pupil size were significantly more pronounced in the IV group compared to the IM group in the initial 3 minutes post-dose. Experimental studies of this type are challenging and thus re-investigation of data obtained from previous studies serves a valuable purpose in providing preliminary information for future studies.

Chapter 7: This chapter discusses the development of the study protocol for the experimental heroin overdose study (described more fully in chapter 8). As part of the development process, consultations were conducted with researchers and clinical colleagues, as well as service users. This chapter also discusses the clinical trial procedures that were involved in setting up the trial itself. Many obstacles were experienced throughout the trial setup and even during the initial data collection period. It is thus important to examine the difficulties and realities of conducting these types of experimental trials which are challenging despite their high level of regulation.

Chapter 8: In this final research chapter, an experimental study of heroin overdose using a dose-incremental, single-blind, within-subject design is described, reporting on investigation of the effect of risk factors (increased dose of diamorphine and familiarity of setting) on physiological and psychological measures in tolerant users. In-depth analysis on three participants as part of a case series presentation in this chapter aims to demonstrate the interim results of this ongoing clinical study. In two of the participants, there appeared to be some effect of dose increases but in-depth analyses showed that one of these individuals had disturbed baseline measures prior to drug administration. The third participant administered his heroin intramuscularly and signs of respiratory depression were less pronounced than those of the other participants, however, there appeared to be some less severe signs of respiratory depression.

The research presented in this thesis represents hugely important pieces of exploratory work captured through realistic using scenarios on which are only being conducted now despite some of these questions having needed attention for many decades. Experimental study of opioid overdose requires attention for better harm reduction approaches to reduce risk of overdose, but this type of experimental study has rarely received much attention. It is worth stating that diamorphine has existed as a medication for over 130 years and has been used in the treatment of heroin addiction for a century, i.e. since before the Rolleston Committee in 1926. Further, opiate addiction treatment services and heroin clinics have existed to a greater or lesser extent, for approximately 50 years. The question that is important but rarely considered is why so few similar studies have been conducted. The likely answer is that they have not been examined precisely because of the very nature of the drug being studied (i.e. heroin). There is something circular and counter-productive about this situation. For example, in the USA, public and regulatory concerns about heroin make it almost impossible for researchers to study the effects of diamorphine (and so other opioid medications such as hydromorphone are used as surrogates for heroin). In fact, diamorphine is not recognised by the Food and Drug Administration (FDA) as treatment for opioid users. In the UK, despite the recent and necessary strict clinical trial regulations, this type of study is nevertheless possible.

9.2 Strengths and Weaknesses of the Thesis

The strength of this thesis is related to the robust examination of certain factors associated with heroin overdose and in the development and testing of criteria and techniques which lay the foundations for an experimental model of acute opioid overdose. This is the first examination of the effects of increased heroin dose on overdose vulnerability in a realistic heroin-using scenario.

There are three main weaknesses in this thesis. Firstly, the inability to complete the originally-envisaged larger study described in Chapter 8 due to administrative and bureaucratic obstacles highlighted in Chapter 7. It is expected that, beyond the work described in this thesis, this study will continue to recruit participants to complete the anticipated sample size that I plan to continue as a post-doctoral researcher. Additionally, further amendments to the study will also allow testing of different routes of opioid administration as well as different measurement tools. It is thus likely that this issue can be resolved.

Secondly, all the studies reported in this thesis had small sample sizes (n=3-20), from which it is difficult to generalise or to formulate large-scale conclusions. Conducting detailed physiological studies is time-consuming as they gather many variables. They are also subject to a high level of attrition due to the within-subject designs, substantial burden on, or simply a lack of, available participants. These types of physiological studies tend to involve a within-subject design and thus, data reported in this thesis constitute exploratory work. However, testing of generalisability to other opioid users is yet to be conducted and should be the focus of future studies.

Thirdly, this thesis brings together the two very different disciplines of Addictions Sciences and Respiratory Medicine. My supervisors are experts in their respective fields, however, as a result of their respective disciplinary orientations differing degrees of importance were given to different aspects of the findings. This made for interesting discussions but also produced conflicts as to the significance of certain issues. I instigated several discussions with supervisors and the study team on aspects of the studies that were particularly interesting and/or of concern. For example, the significance of apnoeic episodes and the length of pauses in breath caused surprise as well as concern. Some of the wider literature on this issue has been raised in Chapter 8. The degree of abnormality for opioid-using individuals was the predominant point of discussion. This highlights an uncertainty in the interpretation of results that should be considered as part of the process of developing an approach to a complex and truly multi-disciplinary investigation.

9.3 Implications for Clinicians

9.3.1 Issue of Multi-Morbidity

As discussed in chapters 3 and 5, it is widely understood that people with mental health conditions have increased risk of physical ill-health, delayed diagnoses and higher mortality rates (Davies et al., 2014). Respiratory conditions potentially contribute to the high mortality figures and it has been noted that better pathways need to be enabled to screen for, and treat, health conditions including lung disease (PHE, 2017). Furthermore, the issue of underlying pulmonary morbidity in individuals who are at risk of opioid overdose is an issue that requires careful clinical assessment and complex service planning (ACMD, 2016).

A great deal of the existing literature relates to asthma and heroin inhalation (Cygan et al., 2000; Hughes & Calverley, 1988; Krantz et al., 2003; Levine et al., 2005): however, very little is actually known of the link between heroin administration and lung disease, let alone overdose risk. There is a need to establish a stronger connection between clinical and experimental investigation of the respiratory system with opioid-induced respiratory depression and overdose risk. In addition to the brief report (Jolley et al., 2015a) on the prevalence of lung disease in a drug and alcohol treatment centre showing that 38% of clients showed signs of COPD (a majority of whom had either injected or smoked heroin), there are a further two studies showing a relationship between impairment of lung function (using either measures of Forced Expiratory Volume in the first second or CT scan of the lungs) and smoking heroin (Buster, Rook, et al., 2002; Walker et al., 2015).

As mentioned in chapter 5, more robust interventions need to exist to better identify chronic respiratory diseases in the opioid-using community. Even if overdose is not a potential risk/consequence, there is a clear requirement for this from the perspective of general health and well-being of this, often multi-morbid, population. In relation to this, drug users who smoke have a heightened risk of premature death than non-smokers (Hser et al., 1994); among drug users, opioid users appear to show the highest rates of smoking (Bowman et al., 2012; Clemmey et al., 1997; Guydish et al., 2011; Pajusco et al., 2012; Tacke et al., 2001). More targeted nicotine replacement therapy or e-cigarette interventions for smoking cessation among opioid users could be one way to resolve this. Some studies have evaluated whether contingency management is effective at reducing tobacco smoking among opioid users, and have observed positive results (Dunn et al., 2010; Dunn, Sigmon, Thomas, Heil, & Higgins, 2008; Shoptaw et al., 2002; Sigmon et al., 2016; Tuten, Fitzsimons, Chisolm, Nuzzo, & Jones, 2012), but further work needs to be done in this area.

There was also an issue of unawareness of respiratory disease: in chapter 5, among those that showed signs of lung disease, 62% were unaware and had not previously complained of any respiratory symptoms. One participant in chapter 8 was also another case. While these findings were not part of the original aims of the studies, it is important in the context of issues described in this thesis, as well as the fact that chronic lung disease progresses slowly and can result in a significant burden to the individual. Raising awareness is evidently crucial to resolve this issue. There is work being conducted in this area through lung health screening clinics. One is led by Dr Caroline Jolley in South London, and another group is based in the North West of England, who have assessed feasibility of such clinics in community drug treatment centres. These clinics are an example of strategies that can deliver relevant screening at point of access of drug treatment. In these clinics, a lung health screening to record symptoms that might indicate lung health problems as well lung function tests and oxygen readings are taken (Burhan et al., 2018; Jolley et al., 2015a). This work is also relevant to the issues pertaining to smoking cessation, as it is potentially effective approach in targeting relevant individuals.

Other complications of multi-morbidity are discussed further on in this chapter.

9.3.2 Chronic and Severe Respiratory Depression Amongst Experienced and Long-Term Opioid Users

It is understood that there is an increased vulnerability amongst older opioid users (Gao et al., 2016; Pierce et al., 2018) and age is a risk factor for opioid overdose (Bartu, Freeman, Gawthorne, Codde, & Holman, 2004; Darke, Kaye, & Duflou, 2006; Warner-Smith, Darke, Lynskey, & Hall, 2001). However, as mentioned in chapter 5, it is still unclear whether this is a sensitivity to opioids or whether there are other underlying age-related conditions influencing this vulnerability. What appears to be reasonable to state from the data presented in this thesis and from previous research to date is that a significant level of respiratory depression exists amongst various groups: in older and experienced users, in those on oral maintenance medication, in those on diamorphine maintenance who inject intravenously and intramuscularly and with normal and higher-than-normal doses. Some of these specific risk factors have been examined in this thesis, however, the issue of increased vulnerability in older, experienced users is one that requires attention.

In chapter 5, age was found to be inversely associated with neural respiratory drive index (NRDI), indicating that NRDI may be decreasing with age in opioid-dependent users (ODU). However, there were no differences in respiratory depressant measures between a median age split of younger and older users in this study. The duration of drug use was associated with the two measures of carbon dioxide, $ETCO_2$ and $TcCO_2$. It appeared to show that the longer the period of drug use, the higher the levels of carbon dioxide. Hypercapnia, generally present with hypoventilation, is a common effect of opioid use. Further, the duration of drug use, similar to age, also showed an inverse association with NRDI and a positive correlation with the number of apnoeic pauses (lasting longer than 10 seconds) and the level of $TcCO_2$. Thus, the longer the duration of use, the more episodes of respiratory depression were observed. Duration of drug use reported in this study did not take into account any periods of entry into drug treatment; it is a general measure of years of opioid use. Nonetheless, a dampened level of drive, an increase in apnoeic pauses, and a higher level of carbon dioxide is a highly risky situation.

In chapter 8, the three participants were all longstanding heroin users, with an average use history of 43 years, which, for all three, is longer than half of their lifetimes (average age of 61 years old). Although two of these participants experienced more severe impairment, all three did show some criteria of respiratory depression. The two participants who showed severe responses were not aware of this, nor had they any complaints of respiratory-related symptoms or problems. The participant with less severe responses had never experienced an overdose in his use career spanning four decades. One other had taken part in the previous acute heroin study (Jolley et al., 2015b) and had an understanding that his oxygen saturation levels could drop to critical levels. Nevertheless, it is difficult to state whether age had any impactful effect on physiological responses to diamorphine in these individuals.

There are challenges to raising concerns about increased risk of overdose with long-term clients who are established in their treatment and often have stable working lives or a routine that is difficult to impede or to disrupt. Despite being on high doses of diamorphine, there is usually little interference into the treatment for reasons specific to overdose risk as this is an area that is usually well-understood by many in the opioid-using community.

The questions that can be raised here are: what can be done clinically? Should there be clinical intervention or discussion of results with participants from these types of studies? In what other form can these discussions take place? The subsequent section discusses potential clinically relevant outcomes of these findings.

9.3.3 Feedback to Participants: ‘From Participant Back to Patient’

Whilst it was not officially structured in this way, the results of these studies were used to have informal discussions between the clinician and the participant. This was relevant for both studies discussed in chapters 5 and 8. The signals obtained from the studies were used as a form of an evidence-based resource to prompt discussion and provide a visual source to guide the conversation. The discussions were generally well-received but no formal evaluation of these conversations was conducted. Given the complex nature of opioid overdose deaths and the potential overlap between observed respiratory depression and respiratory disease, it is important to provide innovative approaches to engaging users with these issues. Future studies should consider whether it is worth exploring an evaluation of behaviour interventions in parallel with these experimental studies on overdose.

Highly specific behavioural interpretations might be worth developing. In a separate line of study of apparently entrenched injectors, a targeted behavioural/clinical assessment for groin injectors was developed (Senbanjo, Tipping, Hunt, & Strang, 2012). Groin-injecting carries significant risks of injury to the femoral vein and femoral artery, bacterial and blood borne viral infections and more serious complications such as deep vein thrombosis, pulmonary embolism, chronic venous disease, among others (Behera, Menakuru, & Jindal, 2003; V. A. Cooke & Fletcher, 2006; Kozelj, Kobilica, & Flis, 2006; Senbanjo & Strang, 2011; Syed & Beeching, 2005). Groin injectors are usually unaware of these risks and tend not to present for treatment until more serious complications arise (Williams & Abbey, 2006). A clinical service used ultrasound scanning for groin injectors in order to assess this particularly risky practice. In preliminary findings of this work (Senbanjo et al., 2012), it was found that single-session portable ultrasound scanning prompted major changes in injecting behaviour including cessation of groin injecting (Senbanjo & Strang, 2015). Perhaps a similar intervention could be implemented, for the long-term opioid users displaying markers of severe respiratory depression. One main question that arises here would be related to what the desired behaviour change would be – whether this be a reduction in dose, non-intravenous use or a full tapering off from opioids completely. These types of questions need answering in order to establish how these physiological techniques could help in a clinical setting.

There are also points raised in the discussion section of chapter 8 that are relevant to the wider discussion of feedback to drug users. The significance of, and advice in relation to, four main questions were discussed in this chapter: 1) Is it advisable to encourage non-IV routes of administration? 2) How important is it to be aware of the potential masking of lung disease symptoms due to depressant effect of opioids? 3) Can the common cold/flu and chest infection leave users more vulnerable? and, 4) How significant are apnoeic episodes and how can users be appropriately advised users on this? These are all points to consider further.

9.3.4 Measuring and Monitoring Overdose Risk

As mentioned in chapter 5, these types of detailed physiological measurements could potentially be used to identify ‘at-risk’ patients. It is feasible that this could be conducted in patients before treatment and, in the future, could even be used as a means of providing opioid users with better information to make more informed choices regarding treatment. It would be pertinent to understand whether these measures could actually reduce the risk of respiratory depression. Could intensive monitoring reduce risk of significant respiratory depression?

It would be very difficult to conduct a larger scale validation study for the diamorphine-maintained individuals, but this would be possible among clients seeking oral opioid maintenance treatment. However, heroin (particularly street heroin) is usually where most of the risks lie. It would therefore be crucial to examine this in a population of users that are either using street heroin or other street opioids. However, there is a critical ethical consideration with this type of research. The solution to this would be to investigate these questions among users who are prescribed a pharmaceutical equivalent in a controlled setting to develop tools that are practical and can be easily monitored within a home setting or, at the very least, a portable drug treatment setting to provide ease for patients. Further discussion on portable, wearable and practical technologies is discussed further on in this chapter.

9.4 Scientific Implications

9.4.1 A Good Model of Acute Overdose in a Laboratory

The varied responses observed in the heroin overdose study (Chapter 8), as well as the chronic respiratory depression that was seen in the observational study (Chapter 5) enable a distinct understanding of, and attribution of influences on, the physiological and pharmacological underpinnings of heroin overdose.

Chapter 5 shows that investigation into chronic, everyday respiratory depression can be observed without disrupting the individual's treatment pattern or drug using pattern. Chapter 8 describes a greatly in-depth study that has been able to work with a dwindling number of patients from a community of heroin users who often feel insecure about their treatment – and it has been demonstrated that it is possible to work with such participants to conduct crucial investigations into the physiological and subjective responses of increased doses of diamorphine. The ability to investigate critical questions of risk factors of heroin overdose in a reliable, well-designed study has provided a strong opportunity to elucidate some of the long-held questions in the field. Furthermore, the ability to capture as realistic a scenario as possible, given the considerable number of influential factors, is a great strength of the study. Data presented in these chapters illustrate the relative ease with which it was possible to detect respiratory depression.

9.4.2 How Can these Findings Be Accounted for?

Whilst there are very few studies examining detailed physiological responses to diamorphine, there are some studies that have investigated the acute physiological effects of opioids, non-fatal overdoses, and dose response effects.

In clinics where supervised heroin (diamorphine) maintenance is provided, there are occurrences of rare but evident overdose events (Jolley et al., 2015b; Oviedo-Joekes et al., 2009; Strang, Metrebian, et al., 2010). In the UK-based RIOTT clinic, the rate was reported to be around 1 in every 6,000 injecting events (Strang, Metrebian, et al., 2010), and in the Canadian NAOMI clinic this figure was around 1 in 8,000 injecting events (Oviedo-Joekes et al., 2009). Also, in a very different type of setting, Roxburgh et al. examined the frequency and severity of non-fatal overdoses of heroin and oxycodone in a medically supervised injecting centre in Sydney

(Roxburgh et al., 2017). This centre did not provide the medication, but it clinically observed injection events. They used the Glasgow Coma Scale (GCS), pulse oximetry and whether naloxone was administered to define whether non-fatal overdoses had occurred. There were 2,500 overdoses out of a total of 500,000 injections. Heroin overdose occurred at three times the rate of oxycodone during the period and appeared to be more severe in terms of levels of reduced oxygen saturation and consciousness. After adjusting for potential confounders, the authors noted that the clients who had a GCS score of less than 8 and oxygen saturation of less than 85% at initial observation were more likely to have injected heroin. It is interesting that the levels of oxygen saturation were equal to or just under the levels that were observed in data in chapter 8 (two of three displayed levels below 85% and one displayed levels above 85%), and the GCS score demonstrated normal levels of consciousness in every session (i.e. the highest GCS score).

Further studies that have looked at pulse oximetry and specifically heroin maintenance studies showed that even normal doses can sometimes lead to hypoxaemic situations. In some studies, the level of participants' regular dose of diamorphine showed significant changes in oxygen saturation (blood oxygen level) in half of all testing sessions (Dursteler-Mac Farland et al., 2000; Stoermer et al., 2003; Stohler et al., 1999). The previous study on acute effects after administration of heroin showed also similar results to the heroin overdose study (Chapter 8) but that study did not alter opioid dose (Jolley et al., 2015b). This is in accordance with the findings in this thesis and further confirms that respiratory depression can occur despite stabilised doses of administered heroin.

It is necessary next to examine dose-sensitive or high-dose effects of opioids. Whilst minimal, there are a few experimental studies that are comparable to this aspect of the heroin overdose study. Reputable studies have conducted this type of increased opiate dose and have successfully shown that this type of study can be implemented without any serious side effects to the subjects. These experimental studies similarly showed a mixture of expected and predicted findings as well as more unexpected findings.

One study examined the effects of high dose diazepam 0mg versus 40mg in combination with high-dose opioids (methadone and buprenorphine) 100% versus 150% of daily dose conducted by colleagues at the National Addiction Centre (Lintzeris et al., 2007). They examined a variety of physiological and subjective measures, including oxygen saturation, pupil size, respiratory rate and blood pressure as well as subjective measures of drug effects including sedation, dysphoria, euphoria and VAS of drug strength, drug-liking and sedation. The high dose opioid was related to lower SpO_2 levels and psychological performance in the methadone group but did not affect the buprenorphine group. Interestingly, only one participant showed a SpO_2 reading below 90%. Another study focused on the craving effects of a 33% increase in oral methadone to patients who are on a daily dose of methadone (Curran et al., 1999). They showed that this increase was a primer for craving of heroin. There was no examination into physiological effects of an increased dose (Curran et al., 1999).

A Dutch study conducted a double-blind randomized investigation on the pharmacological differences between inhalation (IH) and intravenous (IV) routes of administration of heroin, taking patients from the Dutch Heroin on Medical Prescription Research Project (Rook et al., 2006). Their regular doses alternated between 67%, 100% and 150% (and similar to the study in Chapter 8, they only changed the one dose of the day). More positive subjective drug effects were experienced in the IH group compared to IV despite the lower C_{max} (peak serum concentration of a drug) in the IH group. This study also showed that dose increases had a higher response in subjective effect than dose reductions. This study did not measure pulse oximetry or other physiological measures but noted that blood pressure and heart rate were significantly different from baseline in the IV group and only marginally different between doses in the IH group.

Whilst not specifically on overdose, there have also been some studies on chronic opioid users and lung disease, which also show the great prevalence of comorbidity. Palmer et al. showed that drug users have a significantly higher prevalence of respiratory diseases than matched non-drug user controls (Palmer et al., 2012).

9.4.3 Difficult Discussions Regarding Science and Safety

As discussed in chapter 8, one of the participants in the study (Participant B) showed severe responses to diamorphine in the 110% dose session. A difficult situation developed with regard to the decision of whether or not to re-invite this participant for the subsequent dose increase. This was disputed across two or three meetings and email exchanges among study team members. There were opposing views on how best to proceed. One of my supervisors, a respiratory physician argued that there was a clear safety issue and it would be detrimental to continue increasing the dose of diamorphine for this participant, and that the observed long apnoeic pauses and low tidal volume, along with low levels of SpO_2% were potentially critical responses that did not warrant a further increment. Others, including my other supervisor, an addictions professor, and also, a former supervisor (also a clinical academic), expressed disappointment that this increased dose was not able to be examined as it was considered to have been a potentially good test of whether dose increments truly do have a predictive effect. Additionally, it was seen that strict procedures were in place if any serious adverse events were to occur. In the end the decision was to err on the side of caution and not proceed with the +20% increment. This represents a difficult and interesting dilemma. Chapter 8 also discusses the differing levels of significance of apnoeic episodes and the wider literature on this topic. It is certainly crucial to have these discussions and an understanding that even among colleagues working towards the same aim, there are diverging viewpoints on the relative importance of various components of the study.

9.5 Implications for Policymakers

There have been great efforts to address overdose deaths through public health and policy initiatives. By collaborating with other public bodies, the Office of National Statistics (ONS) annual report on deaths related to drug poisoning in England and Wales, as well as the National Records of Scotland's publication on drug-related deaths (DRDs) in Scotland and the Northern Ireland Statistics and Research Agency (NISRA) contribute to the figures of mortality trends within the UK (NISRA, 2016; NRS (National Records of Scotland), 2018; ONS, 2018). Within these reports, there is often discussion of potential causes behind any changes to the numbers of deaths. Further, in recent years, the government agency (under the Department of Health and Social Care) Public Health England (PHE), the Local Government Association (LGA) representing all of the local authorities in England and Wales as well as the non-departmental Advisory Council on the Misuse of Drugs (ACMD) have contributed to the discussion when changes in DRDs are reported (ACMD, 2016; LGA, 2017; PHE, 2016b, 2017). This thesis raises several questions and issues that should be considered by policymakers. This section will briefly summarise the issues with defining and registering deaths in England, Wales, N. Ireland and Scotland as well as the causes and drivers of deaths in the UK.

9.5.1 Defining, Registering and Comparing Deaths in the UK

As mentioned in the introductory chapters, interpreting trends and patterns in opioid-related deaths are centred on the definitions and methods of recording deaths. The definition of a DRD is:

> Death where underlying cause is drug abuse or drug dependence and deaths where underlying cause is drug poisoning and where a substance controlled under the Misuse of Drugs Act 1971 was mentioned on the death certificate (Christophersen et al., 1998).

Generally, methods of recording deaths are comparable in England, Wales and Northern Ireland (N. Ireland). The system of death registration and certification requires all deaths related to drug poisoning to be referred to a coroner for investigation. Information on the specific substances involved in deaths are taken from the information provided on the coroner's death certificate. In Scotland, the system of registration differs and requires DRDs to be investigated by a 'procurator fiscal' (NRS (National Records of Scotland), 2018). Details from the death registration in addition to information from a specifically-designed questionnaire are used to identify DRDs. A forensic pathologist completes these questionnaires and lists the drugs and solvents found during the post-mortem examination. There are a few issues with the system in Scotland; the main problem is that post-mortem paperwork only asks about the drugs that were 'implicated in, or which potentially contributed to, the cause of death', thus, any death that involved drugs that were not considered to have had been directly influenced by drugs are not included in the opioid deaths data (ACMD, 2016). Deaths coded to opioid abuse also do not include those which resulted from injection of contaminated heroin, which they do in England, Wales and N. Ireland. This is because the NRS can identify deaths which occurred as a result of the use of contaminated heroin. These factors mean that comparison between countries is compromised.

The timing of death registration is also an issue. Registrations in England, Wales and N. Ireland do not occur until the coroner's inquest is completed, which can sometimes take many months or even years. Thus, a death registered in a given year could have actually occurred in the years prior to the registration year. In England & Wales, the most recent ONS report on drug-related deaths describes a distinct and increased delay in the registration of deaths up to 2017 (ONS, 2018). There was a slight increase of 3% of registered deaths occurring in the preceding years to the report and a median delay of 10 days (ONS, 2018). It is difficult to state whether this difference relates to any difference in the death data for the 2017 registered deaths, but it is interesting to note. In Scotland, on the other hand, the death registration includes deaths that are almost always ones that occurred in that year. Thus, again, comparing data becomes more compromised.

Despite these differences, measurements of opioid-related deaths right across the UK involve a high-quality certification system that use common International Classification of Disease coding. There is, however, a particular need to improve comparable information from toxicological tests carried out in post-mortem examinations and also to record whether the people who die were currently receiving a medical prescription for an opioid (ACMD, 2016). Further, whilst 'consistent and useful', there are many flaws in the current collection methods that mean trends over time are difficult to interpret (ACMD, 2016). It is currently impossible to assess whether the increase in deaths involving polydrug use (including opioids) is an increasing trend of use or is alternatively a result of better identification and recording. To capture this type of information would further our understanding of the potential complex treatment needs of users. It is also related to the data presented in chapter 5 on the prevalence of lung disease in a long-term opioid-using population, highlighting the issue of co-morbidity. The current definitions also do not lend themselves to capturing the wider burden of opioid use on infections and chronic diseases, given the issues discussed earlier and in previous chapters of ageing, complex needs and multi-morbidity (RCPsych, 2011). It is important to be able to assess this in order to be able to provide better and more targeted service planning. The ACMD's apt recommendation - that there should be greater standardisation of coroners' reporting of DRDs and non-fatal overdoses from local to national systems and through the various channels of reporting - is a welcome contribution to the policy debate (ACMD, 2016).

9.5.2 Causes and Drivers of Opioid-Related Deaths in the UK

The causes of the recent increases in opioid-related deaths in the UK have been discussed in detail in the introductory chapters. Examining the causes through a wider lens allows reflection on potentially impactful factors. There are four potential causes and drivers of the changes in numbers of opioid-related deaths in UK (ACMD, 2016):

1. The ageing of the heroin-using population;
2. Changes in the availability and purity of heroin at street level;
3. Changes in the provision of drug treatment;
4. Socio-economic changes.

Two of the main drivers listed are examined by this thesis: ageing and purity. Previous literature has shown that heroin users appear to become more vulnerable to death from overdose as they age, and this is exacerbated by risk behaviours such as smoking, chronic alcohol use, polydrug use, poor diet and lack of exercise (etc.) (Darke, 2016; Merrall, Bird, & Hutchinson, 2012; Pierce, Bird, Hickman, & Millar, 2015). Reflections on data related to age from this thesis are mentioned earlier in this chapter.

In relation to the issue of purity and the Heroin Drought in 2011/12 where purity levels dropped and then increased at street level, there were reports that during this time, some stopped using or felt effects from the adulterants (Hallam, 2011; M. Harris et al., 2015). The after-effects of the Heroin Drought on purity and availability of heroin at street level was suggested to have had a direct impact on the number of opioid-related deaths during the subsequent years (Hallam, 2011; M. Harris et al., 2015), but very little investigation has been conducted on the UK heroin shortage, at least in comparison to the well-documented Australian shortage of 2000/2001 (Bush, Roberts,

& Trace, 2004; Degenhardt et al., 2005; Degenhardt, Conroy, Gilmour, & Hall, 2005; Dietze et al., 2004; Maher et al., 2007). Related literature on the issue of unknown purity as a risk factor for overdose was described in more detail in chapter 3, where evidence in support or opposition is uncertain. Data from chapter 8 in this thesis show a varied response to differing doses of pharmaceutical heroin. Continuation of this type of investigation is crucial to elucidate the significance of purity. Beyond this, it may be that availability and price may be more impactful to the number of deaths than unpredictable purity fluctuations but this would need further investigation (ACMD, 2016; Harris et al., 2015). In any case, any period of shortage or 'drought' and adulteration probably requires heightened and careful service provision (Harris et al., 2015).

With regard to treatment-related issues, it has been discussed that periods of both entry and cessation into and out of treatment are associated with increased risk of overdose and death (Cornish et al., 2010; Pierce et al., 2016). There are data from England that show an increase in deaths among people who had recently left treatment (PHE, 2016a). Most recently, a 14% increase of people who died whilst in contact with treatment services was reported by Public Health England (PHE) (PHE, 2016a). It would be important to specifically examine this increase in people who have died whilst in contact with drug treatment, through toxicological or review-type investigation, to find out whether there are any points of note or for further exploration.

In relation to socio-economic factors in the UK, drug death rates are substantially higher in the most deprived areas, which may reflect the prevalence of problematic heroin use in these areas (ACMD, 1998; Rhodes, 2009). Life expectancy between the richest and poorest has been growing since 1993 (Mayhew & Smith, 2016). Furthermore, financial hardship and suicide risk (Barr, Taylor-Robinson, Scott-Samuel, McKee, & Stuckler, 2012) and DRDs (Bogdanowicz et al., 2016) are known to be related. Further, areas that experienced the highest rates of DRDs have also experienced the greatest reductions in functioning for local authority services and welfare benefits for working-age adults (Beatty & Fothergill, 2016; Hastings, Bailey, Bramley, Gannon, & Watkins, 2015).

Overall, opioid-related deaths are clearly not straightforward and evidently require more complex and innovative approaches for research and prevention. Additionally, there are factors beyond that of the data and subjects discussed in this thesis. However, future policy-related solutions must be considerate to a wide range of factors and thus, it is important to consider the connecting drivers of opioid-related deaths.

9.6 Improvements for Future Work

There were three main practical issues in the measurement phase of the study sessions in the studies presented in chapter 5 and 8 that potentially led to the participants not feeling as comfortable and relaxed as they could have been or data collection not being as efficient as it could have been.

9.6.1 Frequent Intervening and Number of People Present During Monitoring

For the heroin study described in chapter 8, the issue of intervening/interrupting the participant during the study session for the purpose of collecting data was a consistent topic of discussion among the study team members, from the initial drafting of the protocol up until the present. In order to obtain subjective drug measures and pupil size, researchers were required to engage and interact with the study participant to take these measures. The initial first few minutes are the most crucial in an intravenous dose administration. The steps involved were: baseline measure with a face mask, injection (if self-injecting, sometimes the face mask needed to be taken off because of visual interference), initial subjective measures, and then measures again at 3 minutes. Considering that there were many procedures in this period of time, in some cases it was thought to be somewhat disruptive to the continuous monitoring of respiratory measures. Improvements were made in order to smooth the process (e.g. the nurses who recorded the observer ratings such as the Glasgow Coma Scale - that ask questions about verbal communication and motor abilities - minimised their intervention and limited their questioning to the essentials). Thus, with each study session, this battery of recordings in the initial first few minutes became much smoother.

There were also issues in relation to the number of people in the room during the monitoring session. As part of diamorphine prescribing regulations, it is required that two nurses (or medical professionals) are witnesses to the preparation of the medication as well as to the administration of the medication. Thus, two nurses were always present in the room, in addition to the study doctor, researcher (myself) and sometimes the PI, along with other interested members of the study. Great effort was made to minimise the number of people in the initial first few minutes of monitoring to only include the required people for the study. However, in a handful of cases, there was slight apprehension from the participant about the considerable number of observers. The results did not appear to show that the participant was more roused than other sessions, but this remains a consideration for future work.

That said, the accounts from participants suggest that they did not experience any major degree of unease. As discussed in chapter 8, they were asked at every visit whether the effects of the drug appeared to be affected by the setting and were asked to compare their experiences to previous visits in the study. None of the participants felt that the overall experience differed from their usual experience at home. It must be stated that, as patients who had been on injectable diamorphine prescriptions for many years, these particular participants are more likely to be used to administering their diamorphine in a clinical, hospital setting than their street-using peers.

9.6.2 Electrical Noise and Subjective Nature of EMG Signal Analysis

There are several sources of variation in the signal of EMG_{para} that were discussed in the Methods chapter (Chapter 4). One of the potential sources is in the anatomical differences which can influence the position or orientation of the electrodes relative to the muscle. After recording the signals in the study, offline analysis includes detecting and excluding contaminated signals which is performed manually by selecting signal samples for analysis after visual inspection of the signal. However, computer algorithms do exist to reduce the time required for analysis and the subjective nature of EMG signal selection. These algorithms are not commercially available and thus, were not utilised in this thesis. However, it would be instructive to incorporate these types of methods, which include reducing or eliminating the QRS complex of the ECG and selecting uncontaminated EMG_{para} following objective determination of the degree of signal contamination. This is relevant to all studies in this thesis.

9.6.3 Potential Solutions to the Issues

A potential solution to some or all of the aforementioned issues would be to measure in a closer environment to the participant's usual scenario. Usually this would be within the home. Thus, consideration should be given to developing three potential methods:

1. Mobile versions of the measures where reliable data can be extrapolated. As discussed in the next section, this type of research is still in the early stages of development and requires many more pieces to the puzzle. However, this would be the most suitable as it would be

independent of researchers, it could measure continuously wherever the participant was and would be less burdensome.

2. To be able to transport the measures to the homes of the participants. Currently, this is an impractical technique as the equipment is very heavy and not made for use outside of a laboratory, however:
3. There are tools that are being developed as more practical ways of measuring physiological responses to opioid administration. For example, an automated measure of EMG_{para} using a machine for use among patients with severe COPD (Suh et al., 2015). From a physiological perspective, the manual data acquisition of EMG_{para} and SpO_2 and $ETCO_2$ allows one to explore the data in more detail and with much more reliability. For the purposes of these initial studies, it may not be suitable to use automated machines but future studies could potentially incorporate them. Further, some of the equipment used in the current study are easy to transport, e.g. TOSCA and SpO_2 machines are smaller and lighter.

9.7 Future Research

9.7.1 Using the Experimental Model for Other Important Questions

The methods and measurements presented in each of the data chapters in the thesis represent a robust method on which to base further related questions. This section will highlight some of the rationale behind important further research questions that could arise from this model of opioid overdose.

9.7.1.1 Other Opioids

The growing rate of fentanyl overdose deaths is becoming, or in some cases has become, a considerable concern. As already described in chapter 1, in the USA, it is estimated that nearly 40% of heroin-related deaths involved fentanyl, with many unaware that fentanyl was what they had consumed (Frank & Pollack, 2017) (see Chapter 1). According the most recent figures, in New York City, fentanyl was the most common substance involved across all overdose deaths (57% of deaths) in 2017 (NYC Department of Health and Mental Hygiene, 2018). In the UK, although the numbers are small, a 29% increase in fentanyl deaths was observed from 2016 to 2017. The total number of deaths for 2017 was 75. It has been suggested that similar mixing of fentanyl into heroin might be occurring in the UK as it is in the USA and Canada (ONS, 2018). The questions here would be: are there any potentially safe doses of fentanyl? How does illicitly manufactured fentanyl differ from pharmaceutical fentanyl in its clinical effects? Is there an interaction between heroin and fentanyl in their respiratory depressant effect? This would be a difficult study to perform but fentanyl is a medically used drug with safe dose ranges and is considered to have a good therapeutic margin (Kanowitz, Dunn, Kanowitz, Dunn, & VanBuskirk, 2006).

In relation to hydromorphone, a Canadian study centred in a supervised clinic that provided diamorphine and hydromorphone, in a similar method to the RIOTT study in the UK, also examined whether the clients could distinguish between hydromorphone and heroin (Oviedo-Joekes et al., 2009). Interestingly, the clients could not distinguish between the two, which raises the possibility of many important clinical benefits, for example, giving more choice to users on their treatment as well as overcoming regulatory issues. In addition, the question for future work within this experimental model is whether or not hydromorphone is safer in terms of respiratory depression compared to heroin.

Buprenorphine has been discussed in more detail in the introductory chapters as well as in chapter 5. Buprenorphine is considered to have a lower risk of respiratory depression and overdose rates compared to methadone and other OST medications, showing a ceiling effect (Dahan et al., 2006; Strang et al., 2017; Walsh, Preston, et al., 1994) but it is well-known that buprenorphine deaths do occur (Hakkinen, Heikman, & Ojanpera, 2013). No differences in physiological responses between buprenorphine and methadone were observed in the observational study in this thesis (Chapter 5). It is conceivable to examine buprenorphine further in similar studies, or to expand the observational study in chapter 5 to allow for examination of a larger sample of users.

9.7.1.2 Other Routes

Testing the differences between IM and IV administration further within the same subjects would be an effective way of measuring whether these routes do actually lead to differences in physiological and subjective effects within subjects. As highlighted in chapter 6, there is a good reason to do this. Further, as highlighted in chapter 8, plans to do this are already underway. The facilities, staff, equipment and administrative procedures have progressed in such a way that allow adaptive changes to the current protocol and add further questions to the study. An application to Ethics will be made in order to re-invite the same participants from the study in chapter 8 that have been examined thus far to undertake the same sessions but with administration of a different route of injection, i.e. IM instead of IV or vice versa. This would lead to a strong within-subject design.

As mentioned in chapter 6, it would also be important to examine the difference between IV use of heroin and other routes of administration such as chasing or snorting. This would be difficult to do among people who are prescribed injectable diamorphine but potentially likely among illicit heroin users. As mentioned previously, this type of study would ethically be more difficult to establish but would be a valuable contribution to the understanding of heroin overdose.

9.7.1.3 Reversal

A positive aspect of opioid overdose is that it can actually be reversed and there is a huge body of related research on this (Alqurshi et al., 2016; McDonald, Campbell, & Strang, 2017; McDonald et al., 2018). There has been development, refinement, testing and advocating for, the pre-provision of naloxone in the community (take-home naloxone) to reverse opioid overdose and thereby prevent deaths. Naloxone is a remarkable rapid-acting mu-opioid antagonist (and is an everyday medicine in anaesthetic rooms, emergency departments and ambulances). However, there are questions within this area that could be answered through the use of a model of overdose. A missing element to current experimental studies of naloxone is the conduct of experimental studies involving actual opioid users instead of healthy volunteers. This is clearly a challenging area which most people have regarded as impossible but would give a potentially very important perspective. There are some preliminary responses on this topic from recent qualitative interviews about factors associated with engagement with the research (Neale, Tompkins, McDonald, & Strang, 2018). There is no question that this is difficult, but it is possible if the studies are designed appropriately. The questions that arise from this are related to determining how effective naloxone is at reversing different opioids, and whether there is a dose-response relationship in the reversal. Furthermore, we need to consider the ways in which naloxone reverses opioid action. Should overdose only ever be reversed enough for respiratory function to re-start? These are crucial questions for which answers are needed, and the answers will directly influence the manner in which emergency naloxone is administered, both by medics and paramedics and also by lay responders.

9.7.1.4 Stages of Treatment

It is an important to question whether an individual who has tapered their opioid substitution medication, to be either fully opiate-free or at a lower stable dose, displays similar chronic respiratory depression criteria to those discussed in chapter 5. It could be hypothesised that, if someone has tapered off their opioid medication and is not on any opioid, they would show less of an everyday respiratory depression response to that which we have observed. Similarly, is there a difference before someone is started on treatment? Is treatment genuinely protective against respiratory depression? It would be logical to presume that oral opioids would be more protective than injectables but a large scale, case-control study would be required to determine this.

9.7.1.5 Co-drugs, Particularly Other Depressant Drugs

It is understood that, even with a well-tolerated dose of heroin, the presence of other central nervous system depressant drugs, such as benzodiazepines, can prove fatal (Darke, 2011). As described in chapter 2, alcohol and benzodiazepines are the most commonly co-administered drugs. Polydrug use is possibly an extremely important risk factor in overdose deaths. In terms of the physiological effects, benzodiazepines have been shown to decrease oxygen saturation significantly in the presence of opioid substitution drugs such as methadone and buprenorphine (Lintzeris et al., 2007, 2006). Furthermore, co-administration of a depressant greatly increases the likelihood of a fatal situation because it potentiates the respiratory depressant effects of heroin. In the presence of depressants, a normal dose of heroin may be fatal (Darke, 2011). However, whether this apparent increased risk of respiratory depression occurs via a potentiation of opioid effects or a synergistic action of more than one depressant is not well understood. Plans to incorporate a benzodiazepine element in the study in chapter 8 have been described in the process chapter (Chapter 7). There were discussions with service users about the feasibility of conducting this type of study. None stated that it would be too risky or unfeasible. The reason why it could not proceed came down to the unexpected cost of placebo drugs and the need to focus on diamorphine. Future studies could incorporate costs in the budgeting stage of the study development. It would be pertinent to study the combined effects of opioids and benzodiazepines.

9.7.2 Wearable Technologies

An exciting possibility for clinicians and the wider public health domain is that, in future, these data may be able to drive technology and to allow for an early detection of risk of opioid overdose. The eventual aim would be for these tools to be implemented in a method that is fast-responding and life-saving. The next section will outline the future work that should be taken forward with these data.

Alongside this work to further understand the physiology, there is definitely scope for developing the wearable technology aspect of this work. As described in chapter 5, there are already some early developments with this type of investigation. As this thesis is being written, a plan to implement an exploration into wearable measures into the current study is being conducted. There are discussions with a colleague in the USA about analysing, in real time, the distinctive 'motion signatures' that may underlie the process of preparing for and administering, an injection of heroin. It would be particularly important to be able to capture the actual self-injection manoeuvres involved. Additionally, although there are many issues with pulse oximetry as a delayed measure of respiratory depression, there is a view that with the correct type of sensor, it could be possible to detect reduced levels of oxygen saturation via a wearable and wireless sensor. The practical issues around such measurement require further exploration but it is a viable course of experimentation to undertake.

Furthermore, there are discussions with colleague in Canada who specialise in fibre-optics and have developed practical methods of measuring respiratory arrest and even respiratory depression through a wearable sensor built into a t-shirt (Guay, Gorgutsa, Larochelle, & Messaddeq, 2017). There are current plans to allow these t-shirts to be tested in the overdose study here within our group in the near future. If these t-shirts are effective at reliably and sensitively recording respiratory depression, the logical next step would be to incorporate an algorithm for an alarm that would be triggered by a Bluetooth sensor. This could also involve the transmission of geo-positioning for the purpose of informing emergency services.

As discussed in chapter 5, deaths from opioid overdose could be prevented if the onset of the overdose were detected in time. Informing future research into practical wearable versions of these measures in order to reliably monitor and ultimately prevent fatal overdose events is crucial. Future studies need to concentrate on taking this model further, i.e. investigating how can we predict vulnerability to a fatal overdose.

9.7.3 Investigating Genetic Variability

The theory related to genetic variability and overdose risk is rooted in the OPRM1 gene which is related to mu-opioid receptor sensitivity where the respiratory depressive actions occur. It is thought that there is some involvement in individual variability of drug metabolism (Befort et al., 2001; Chidambaran et al., 2015; Goldstein, VanDenKerkhof, Sherlock, Sherlock, & Harper, 2001; Manini et al., 2013). There is a great deal of literature on pain responses and alcohol consumption in the presence of this polymorphism, but there is limited, if any evidence on physiological responses in opioid overdose (Bilbao et al., 2015; Ray & Hutchison, 2004; Sloan et al., 2018; Yu et al., 2018).

There had been discussion of including a genetic component within the study presented here and this has been discussed in more detail in chapter 8. Ultimately, a large sample size is required see an effect within a genetic study. This would clearly not be feasible amongst diamorphine-maintained patients in the UK. There could be some scope to expand this type of study to other opioid prescribed patients, or to street heroin users, but this would be a separate exploration.

Conclusion

Despite knowledge of respiratory depressant effects of opioids, the actual vulnerabilities to, and mechanisms of, overdose are still not well understood. There is no gold standard measure of respiratory depression, and methods used in clinical settings such as anaesthesia involve the use of invasive techniques, or techniques that are not sensitive to the impact of chronic lung disease. Collaboration between Addiction Sciences and Respiratory Medicine, that I have been a central part of, has allowed the development of reliable and sensitive techniques to measure respiratory depression among long-term opioid users. It has thus been possible to test risk factors that have been commonly thought to be involved in overdose risk but never thoroughly investigated. Increased purity (equivalent to increased dose), routes of administration, setting, differing opioids and underlying chronic lung disease have all been explored in this thesis. The key findings of this thesis are threefold: 1) that experimental research into heroin overdose is possible; 2) that respiratory depression exists across a broad clinical sample – including amongst older and experienced opioid users on various doses and via differing routes; and 3) that there is an additional respiratory system 'burden' of underlying lung disease in long-term users. It has also been possible to lay the foundation for future research to carry forth the baton and develop innovative approaches to measuring risk of overdose.

Opioid-related problems and deaths are continuously present in the UK and unfortunately, the recent increases in trends are not only the highest on record but also, do not appear likely to diminish any time soon. This is also true for the USA which is experiencing one of the most severe epidemics of overdose deaths that has ever been seen in record numbers (both total and per capita) (Sanger-Katz, 2018). Moreover, restrictions to the NHS infrastructure and the socio-economic impact of post-2009 Britain leave colossal challenges to drug treatment services, as well as to allied primary and emergency care services that are fundamental in maintaining healthy lives of drug users.

The message is clear that there is no simple solution to this complex issue of overdose but persisting and developing work in this area to etch away at questions and draw alongside other health-related phenomena is essential. Beyond this, good research is the very least that drug users deserve in the face of the adversity, prejudice and stigma that they still continue to face.

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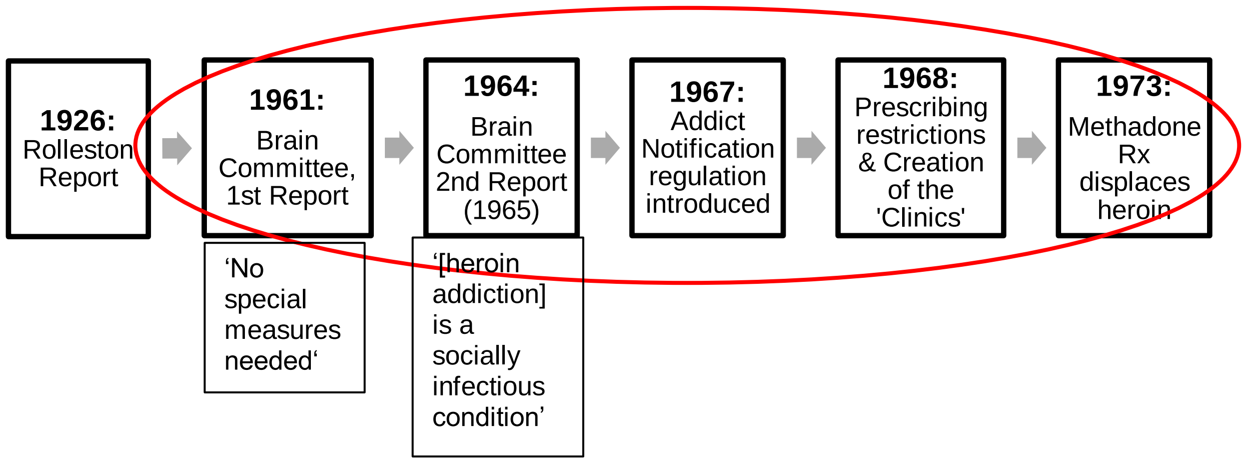
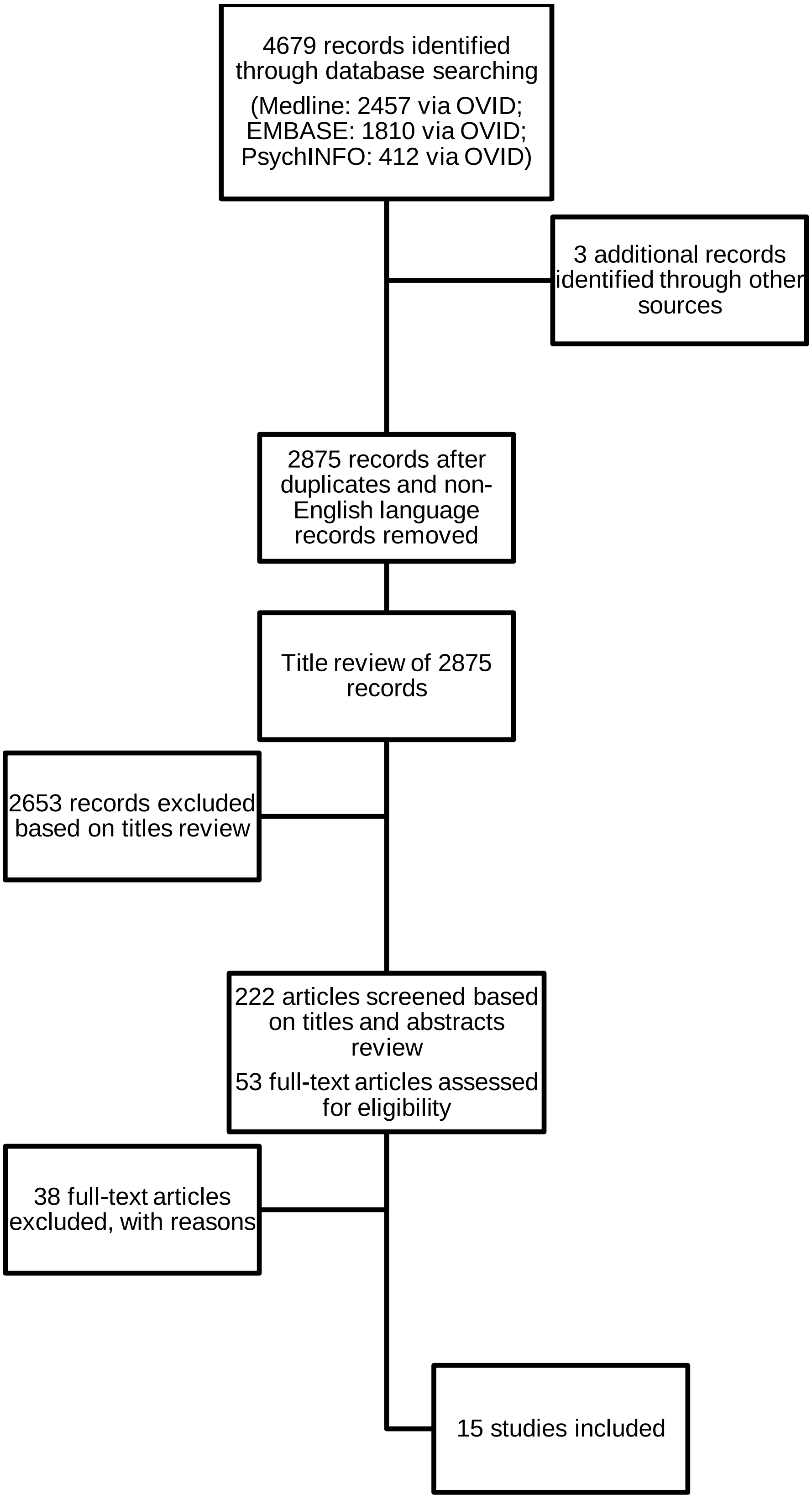
Appendix A. Literature Review

Appendix A-1: Timeline and period of interest for Historical Review



Appendix A-2: Flowchart of database search



Appendix A-3: Search Strategy

1. exp heroin dependence/ or heroin dependen*.mp.
2. exp drug dependence/ or drug dependen*.mp.
3. exp opiate addiction/ or opiate addict*.mp.
4. diamorphine/ or heroin addict*.mp.
5. maintenance therapy/ or heroin maintenance.mp.
6. opiate/ or opiate prescription.mp.
7. Heroin treatment.mp.
8. Addicted to heroin.mp.
9. drug abuse/ or drug addict*.mp.
10. or/1-9
11. follow-up.mp. or exp follow up/
12. observation*.mp. or exp observation/
13. exp case study/ or case.mp.
14. year*.mp.
15. exp mortality/ or mortality.mp.
16. exp death/ or death*.mp.
17. or/11-16
18. 10 and 17
19. Limit 18 to year=”1965-1975”

Inclusion criteria:

1. Reporting period of study must be between the years 1960 and 1975
2. Study population includes patients prescribed pharmcaceutical heroin as part of heroin addiction treatment
3. Text of article must be English
4. Outcome reported must include mortality

Exclusion Criteria:

1. Article texts not in English
2. Reporting period outside of the time period of interest, 1960 to 1975
3. Outcome reported in the publication not mortality

Appendix B. Heroin purity and heroin-related deaths

Studies correlation heroin purity with heroin-related deaths.

Author (Year)	Study Location	Study Period	Fatal/Non-Fatal	Study Details	Main Findings
Bammer (1995)	Canberra, Australia	Christmas 1992	Fatal	Case report (n=3)	No clear role of heroin in fatalities. Purity not involved in these deaths.
Darke et al (1999)	SW Sydney, Australia	Feb 1993 to Jan 1995	Fatal	Time Series Analysis/Observational (n=322 heroin samples. N=61 deaths)	Moderate but significant correlation (0.57) between mean purity of heroin and overdose fatalities.
Risser et al (2000)	Vienna, Austria	1987-1995	Fatal	Post-mortem and seizure analysis	No significant relationship between heroin-related deaths and heroin concentration seizures in that time.
Degenhardt et al (2004)	NSW, Victoria & South Australia, Australia	1996-2003	Fatal & Non-fatal	Observational	Overdoses decreased by 40% (fatal) and 85% (non-fatal) during heroin shortage period.
Degenhardt et al (2005)	New South Wales, Australia	Jan 1995 - June 2003	Fatal & Non-fatal	Time series analysis on overdoses from hospital emergency departments	Fatal and non-fatal heroin overdoses decreased during the heroin drought. Heroin supply reduced related deaths and didn't cause an increase in other drug-related deaths.
Risser et al (2007)	Vienna, Austria	1999	Fatal	Time series - Post-mortem, emergency incidents, and seizure analysis	No relationship between heroin related incidents and fluctuations in purity of street heroin.
Toprak & Cetin (2009)	Istanbul, Turkey	1990-2000	Fatal	Post-mortem and seized opium derivatives	Weight of heroin and number of seizures, but not purity, were associated with heroin-related deaths.
Horvath et al (2013)	Budapest, Hungary	1994-2012	Fatal	Post-mortem	Slight positive correlation between overdose deaths and mean heroin street purity.
Unick et al (2014)	Various locations, USA	1992-2008	Fatal & Non-Fatal	Hospital admissions versus purity and price	Purity not associated with heroin overdose but decreased price per gram is.

Appendix C. Additional Data and Resources (Chapter 5)

Appendix C-1: Personal characteristics of all 20 ODU participants.

Number	Group	Age group	Gender (M/F)	BMI (mg/kg^2)	Lung disease severity	Acute OD?	Frequency of OD	Smoking status	Smoking pack year
1	ODU	50s	M	30	Healthy	Yes	3	Current	10
2	ODU	40s	F	25.3	Healthy	Yes	7	Current	7
3	ODU-LD	40s	M	21.1	Mild COPD	Yes	4	Current	12
4	ODU-LD	30s	M	18.7	Mild COPD	Yes	3	Current	8
5	ODU	50s	M	37.8	Healthy	No	0	Ex	31
6	ODU-LD	60s	M	27.95	Severe COPD	No	0	Ex	15
7	ODU-LD	60s	M	19.64	Mild COPD	No	0	Current	9
8	ODU	40s	M	31.4	Healthy	Yes	3	Current	17
9	ODU	40s	F	32.7	Healthy	Yes	1	Ex	19
10	ODU-LD	50s	M	27.7	Moderate COPD	No	0	Current	91
11	ODU-LD	40s	M	19.74	Moderate COPD	Yes	10	Current	30
12	ODU-LD	50s	M	32	Mild COPD	No	0	Current	15
13	ODU-LD	40s	F	29	Asthma	Yes	2	Current	10
14	ODU-LD	30s	M	34	Severe COPD	Yes	3	Current	5
15	ODU-LD	40s	M	19	Severe COPD	No	0	Current	15
16	ODU	40s	M	25	Healthy	Yes	1	Current	25
17	ODU-LD	40s	M	23	Mild COPD	No	0	Current	37
18	ODU	30s	M	29	Healthy	Yes	2	Current	2
19	ODU-LD	30s	F	24	Mild COPD	No	0	Current	25
20	ODU-LD	60s	M	22	Moderate COPD	No	0	Current	11

Appendix C-2: Drug use characteristics for all ODU participants

Number	First heroin use (years)	Route of preferred Heroin use	Today: Other drugs taken?	General: Other drug use	Alcohol screen	Cocaine?	Morphine?	Benzo-diazepine?	Meth-amphetamine?	THC?	Meth-adone?	Amphet-amine?
1	19	IV	No	Alcohol & cannabis	No	Yes	Yes	No	No	Yes	No	No
2	15	IV	No	None other	No	No	Yes	Yes	Yes	No	No	Yes
3	20	IV	No	None other	No	No	No	No	No	No	No	No
4	16	IV	Yes	Alcohol & benzos	No	Yes	Yes	Yes	Yes	Yes	Yes	No
5	27	IH	No	Benzos	No	No	Yes	Yes	No	No	Yes	No
6	15	IV	Yes	Benzos	No	No	No	Yes	No	No	Yes	Yes
7	20	Both	No	Cannabis	No	No	No	No	No	No	Yes	No
8	18	IV	No	Alcohol	No	Yes	Yes	No	No	No	No	No
9	23	IV	No	None other	No	No	No	No	No	No	No	No
10	36	IH	No	Alcohol	No	Yes	Yes	No	No	No	Yes	No
11	16	IV	No	None other	Yes	No	No	No	No	No	No	No
12	25	IH	No	Alcohol & cannabis	No	No	No	No	No	No	No	No
13	27	IV	No	Cannabis	No	No	No	No	No	No	No	No
14	19	IV	No	None other	No	No	No	No	No	No	No	No
15	23	Both	Yes	Cannabis	No	No	Yes	No	No	No	Yes	No
16	43	IH	No	Alcohol	Yes	No	No	No	No	No	No	No
17	15	Both	No	Cannabis	No	No	Yes	Yes	No	Yes	Yes	No
18	20	IV	No	Alcohol & benzos	No	No	Yes	Yes	No	No	Yes	No
19	34	IH	No	Benzos	No	No	No	Yes	No	No	No	No
20	40	IH	No	Cannabis	No	Yes	Yes	No	No	Yes	No	No

Appendix C-3: Treatment characteristics for all ODU participants.

Number	OST	OST dose (mg)	OST in DDD	Current Tx (months)	Years since first Tx	Freq. Tx	Today: OST taken?	Typical freq. of dose
1	Buprenorphine	16	2	1	5	4	No	Supervised daily
2	Diamorphine Injectable	400	unknown	168	20	4	Yes	Split Dose
3	Buprenorphine	2.8	0.35	60	20	2	Yes	Split Dose
4	Methadone	60	1	2	19	15	Yes	Supervised daily
5	Methadone	50	0.83	1	30	4	No	Once daily
6	Methadone	75	1.25	42	45	4	Yes	Split Dose
7	Methadone	40	0.67	24	30	6	Yes	Once daily
8	Buprenorphine	12	1.5	1	12	5	No	Once daily
9	Buprenorphine	8	1	24	25	6	No	Once daily
10	Buprenorphine	4	0.5	2	8	6	Yes	Once daily
11	Buprenorphine	8	1	3	25	16	No	Supervised daily
12	Buprenorphine	6	0.75	12	20	7	No	Supervised daily
13	Buprenorphine	20	2.5	1	9	4	No	Supervised daily
14	Oral Diamorphine	450	unknown	3	16	4	No	Split Dose
15	Buprenorphine	16	2	24	2	2	Yes	Once daily
16	Buprenorphine	12	1.5	12	2	5	No	Supervised daily
17	Methadone	80	1.33	96	8	1	No	Supervised daily
18	Methadone	105	1.77	4	15	6	Yes	Split Dose
19	Buprenorphine	16	2	60	5	1	No	Once daily
20	Buprenorphine	20	2.5	120	21	2	No	Once daily

Appendix C-4: Presence (yes) or absence (no) of respiratory depression criteria between all ODU grouped by prescribed OST.

	SpO_2 < 90% > 10 secs		$ETCO_2$ breaths > 6.6kPa		TcCo₂ > 6kPa		Respiratory Pauses/NRDI > 10 secs	
	Yes	No	Yes	No	Yes	No	Yes	No
Methadone	2	4	4	2	2	4	4	2
Buprenorphine	2	10	8	4	4	8	5	7
Diamorphine Injectable	0	1	1	0	1	0	1	0
Oral Diamorphine	1	0	1	0	1	0	1	0
Total	5	15	14	6	8	12	11	9

Appendix C-5: Gas transfer results for all ODU participants, median (IQR; interquartile range). TLCO: carbon monoxide transfer factor; KCO: carbon monoxide transfer coefficient.

	Value	% predicted
TLCOc	6.75 (5.9-8.6) $mmol \cdot min^{-1} \cdot kPa^{-1}$	71 (63.8-78)
KCOc	1.2 (1-1.3) $mmol \cdot min^{-1} \cdot kPa \cdot L^{-1}$	77.8 (65.5-83)

Appendix C-6: Additional findings for study. Comparison of differences between age (younger and older), OST type, route of heroin administration and smoking pack years (heavier and lighter) with respiratory depression criteria. Mann-Whitney or Kruskal-Wallis Tests were used. Numbers represent p values.

Characteristic	$ETCO_2$ (kPa)	$ETCO_2$ >6.6kPa freq	NRDI (min^{-1})	Resp pauses >10s freq	$TcCO_2$ (kPa)	SpO_2 (%)	SpO_2 < 90% >10s freq	FEV_1/VC% ratio
Age – younger or older	0.35	0.8	0.25	0.52	0.9	0.11	0.4	0.03*
OST type	0.27	0.29	0.56	0.12	0.25	0.25	0.16	0.43
Route of Heroin Administration	0.008	0.28	0.54	0.2	0.32	0.31	0.54	0.49
Smoking pack history – heavier or lighter	0.23	0.3	0.82	0.71	0.94	0.24	0.4	0.66

Appendix C-7: earlobe blood gas results for all groups where applicable, median (IQR). N/M: not measured; pO_2: partial pressure of oxygen; pCO_2: partial pressure of carbon dioxide; HCO_3^-: bicarbonate.

	ODU	**Controls**	**ODU-LD**	**LD Controls**
Baseline SpO_2 (%)	96.1	96	95.5	95.4
pO_2 (kPa), median (IQR)	10.6 (10.5-11.6)	N/M	9.7 (9.4-10.4)	8.2 (7.9-8.5)
pCO_2 (kPa), median (IQR)	5.1 (5-5.5)	N/M	5.3 (5-5.6)	5.1 (4.9-5.2)
HCO_3^- (mmol/L), median (IQR)	24.3 (23.9-24.6)	N/M	25.6 (24.4-26)	26.9 (25.7-27.4)
pH, median	7.4	N/M	7.4	7.4

Appendix C-8: Medical questionnaire

King's College Hospital NHS

NHS Foundation Trust

V2.23/9/16

Date:_____________

Identification:_________________

Medical History

Name: DOB:

Gender F/M

Smoker: Y/N How long:

Breathlessness scale: 0 1 2 3 4 5 6 7 8 9 10

Other medications:

Height:

Weight:

BMI:

Spirometry: Normal Mild Moderate Severe

FEV_1: %predicted

FEV_1/VC: %predicted

OST

Buprenorphine/Methadone/Other Dose:

Duration of this treatment:

No. times in treatment:

First entry into treatment:

Other drug use

Other prescribed drugs:

Other drugs:

Alcohol? Benzodiazepines? Cannabis? Crack? Heroin? Other?

NB: Frequency, dose and route of administration for any other drug.

Details related to previous heroin use

Age of first heroin use:

Have you ever had a near-overdose?   How many times?

Current living situation

Alone/with a partner/children/friends/family/Other

Daily routine

What time did you take your dose today?

What time do you normally take your dose?

Do you split it? If so, how?

What did you have today? Drugs and diet included.

What is a typical day for you?

Urine & Alcohol Screen

Drugs present:

AMP   BZO   COC   MDMA   MTD   OPI   THC

AMP: Amphetamine; BZO: Benzodiazepine; COC: Cocaine; MDMA: ecstasy; MTD: Methadone; OPI: Opiates; THC: Cannabis

Alcohol:

BAC_________mg

Conversion to BAC%

Appendix D. Summary Timeline of Steps in the AOO Study

Step	Date
Protocol Draft	Dec-14
Revisions to protocol and decision on type of study - CTIMP by the MHRA	Apr-15
Full Budget and Costing form	Jul-15
Scientific Review	Nov-15
Risk Assessment Committee Final Decision	Jan-16
Assignment of Sponsorship	Jan-16
Assignment of Clinical Research Associate (CRA)	Mar-16
Arrangement of kick-off meeting	May-16
MHRA application/competent authority application	Jul-16
IRAS completion	Jul-16
Pharmacy contact	Oct-16
Initial Research Ethics Committee (REC) meeting	Oct-16
Response to requested amendments by REC	Nov-16
Full acceptance from REC	Nov-16
Response to HRA review amendments	Jan-17
HRA approval	Jan-17
Sponsorship approval	Mar-17
Database management and creation of database	Mar-17
Initial contact with external agencies	Apr-17
Substantial amendment to include external agencies	Jun-17
Final REC, MHRA, HRA, R&D approvals	Jul- & Sep 2017

Meeting and training the RNs	Dec-17
Ordering equipment, materials and IMP	Oct-17
Validating the database	Nov-17
Green light for recruitment given by Clinical Trials Office	Dec-17
Pharmacy duties and tasks	Jan-18
Recruitment and invitation of participants for study sessions	Feb-18
Data collection	Feb to Aug-18

Appendix E. Additional Data and Resources (Chapter 8)

Appendix E-1: AOO Protocol

EudraCT number: 2016-001877-34

REC: London South East National Research Ethics Committee

Inclusion Criteria

Each subject will be selected according to the following inclusion criteria:

Diamorphine-injecting subjects who have been in treatment for a minimum of one month;

1. Male or female;
2. ≥ 18 years;
3. Capable of providing voluntary written informed consent;
4. A non-custodial stable residence and telephone number;
5. Venous access has to be suitable for intravenous drug administration and cannula insertion;
6. Oxygen saturation reading of ≥92%;
7. Forced expiratory volume in 1 second ratio, predicted % (FEV_1%) of >50% (spirometry);
8. Absence of acute respiratory illness for 6 weeks prior to screening or any study day.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Dependent use of cocaine or amphetamines requiring specific treatment. This will be assessed at Pre-Study Screen.
2. Active significant medical condition (e.g. hepatic failure or severe hepatic disease) as determined by clinical assessment, medical history and as advised by their treating clinician. This will be assessed by the clinical investigator at Pre-Study Screen, for example:
    a. Severe hepatic insufficiency (liver function tests conducted within the last 6 months prior to screening): Patients with clinical features of hepatic failure (e.g. encephalopathy, ascites, jaundice, prolonged bleeding, hypoalbuminaemia and secondary oedema – consistent with

Child-Pugh Classification B or C). Patients with liver disease (e.g. HCV, HBV infection) without features of hepatic failure are potentially eligible.

   b. Severe respiratory insufficiency or the inability to reliably perform physiological tests of respiratory function (spirometry).

   c. Pre-existing renal or cardiac issues that the study physician or treating clinician considers inappropriate for the purposes of this trial.

3. In cases where subjects are able to perform spirometry, a $FEV_1\%$ of ≤50% as confirmed by spirometry at Pre-Study Screen.

4. Oxygen saturation reading of <92% as confirmed by finger pulse oximetry at Pre-Study Screen.

5. Acute illnesses that make participation inappropriate, as assessed by the study physician. Presence of acute respiratory illness within 6 weeks prior to screening or any of the study sessions. This will be assessed during screening and on each study day. If acute illness is present, subject will be asked to return 6 weeks post-acute illness. Acute diarrhoeal conditions caused by antibiotic-induced pseudomembranous colitis or by poisoning will be assessed by the study physician. Assessment at Pre-Study Screen and on each Study Visit.

6. Subjects suffering from acute alcoholism or delirium tremens. This will be assessed at Pre-Study Screen.

7. Subjects who have suffered from head injury or have been with diagnosed phaeochromocytoma. These will be assessed at Pre-Study Screen.

8. Risk of paralytic ileus or biliary colic assessed by the study physician. This will be assessed at Pre-Study Screen.

9. A benzodiazepine prescription that is above the standard therapeutic dose range (e.g. if oral Diazepam above 30mg/daily; BNF, 2016). This will be examined by medical notes at the Pre-Study Screen. A drug test on each Study Visit will be performed to assess whether there is any presence of benzodiazepines that the participant is not prescribed. Concomitant medication check will also be conducted at Pre-Study Screen.

10. Subjects prescribed other contraindicated drugs: monoamine oxidase inhibitors (or within 2 weeks of their discontinuation), 4-quinolone antibacterials, phenothiazines, tricyclic antidepressants, anxiolytics (see above), hypnotics, cisapride, domperidone and metoclopramide, cimetidine and selegiline. This will be assessed at Pre-Study Screen.
11. Alcohol and other drug use on the specific study days. A drug screen (Angelscope) and breathalyser (BACtrack, Xtend®) will be used to confirm additional drug/alcohol use on the study days. A positive drug screen (excluding prescribed drugs) and an excessive blood alcohol content (BAC) (based on the legal driving limit in England & Wales of 0.8g/L) will result in a re-invitation to an alternative study date. This will be assessed on each Study Visit.
12. Current psychiatric diagnosis of major depression with suicidal ideation, psychosis, bipolar disorder, or any psychiatric disorder that would compromise the subject's ability to complete the study. These will be assessed at Pre-Study Screen.
13. At screening and on each study day, if there is a chance that female subjects may be pregnant; subjects will undergo a pregnancy test. A positive pregnancy test will result in an exclusion from the study. In addition, mothers who are lactating, women of childbearing potential who refuse to use adequate contraception and pregnancy tests during the study, or women who are planning to become pregnant during the period of the study will also be excluded. This will be assessed at Pre-Study Screen and on each Study Visit by the clinical investigator.
14. Any other factor that in the opinion of the study physician would make the subject unsafe or unsuitable for the study. This will be addressed at Pre-Study Screen and on each Study Visit by clinical investigator.

NB: clinical and diagnostic assessment will be conducted by the study clinical investigator/physician.

Selection of Participants

Participants will be opioid-dependent patients undergoing prescribed injectable diamorphine (pharmaceutical heroin) treatment with long-term history of heroin injecting use. The minimum time period for current treatment with diamorphine maintenance will be one month.

All patients on diamorphine maintenance between the inclusive ages will be informed of the study by direct clinical care staff. Any potential participant will be further informed of the study details by investigators, have an opportunity to ask questions, be informed of their right to withdraw, and be provided with a copy of the patient information sheet.

If participation is chosen, the PI or co-investigators, in accordance with the Clinical Trial Regulations, the Declaration of Helsinki 1996 and GCP requirements will take consent. A copy of the signed consent will be provided to the participant.

Screening Tests

Measurements at screening will include spirometry (forced expiratory volume in 1 second (FEV_1) and slow vital capacity (VC)) to report the predicted FEV_1% ratio which will indicate the presence or severity of respiratory illness relevant to the study. If the ratio falls at or below 50%, subject will not be eligible for the study. Furthermore, pulse oximetry will also be measured and any reading below 92% will deem the subject ineligible for the study. Vital signs (blood pressure and heart rate) will also be measured.

Additionally, female subjects who are of childbearing potential who may have a chance of being pregnant will undergo a pregnancy test (a urine test). Female participants of childbearing potential will be asked to take contraceptive precaution during the period of time within the study.

Tests Prior to Each Study Visit

A drug screen (a dipstick urine test, Angelscope) and breathalyser (BACtrack, Xtend®) will be used to confirm additional drug/alcohol use on each of the study days. The purpose of the drug/alcohol test is to prevent any potential concomitant acute effects of other drugs that are not described in the patient medical records. Vital signs (blood pressure and heart rate) as well as oxygen saturation (SpO_2%) will also be measured.

All testing will be immediate and any used equipment will be discarded immediately after use. No samples will be stored or analysed further.

An assessment of pregnancy status will be addressed at each study visit by the clinical investigator.

Presence of Acute Respiratory Illness

If acute respiratory illness is reported to have occurred within 6 weeks prior to screening or any study session, the subject can be re-invited 6 weeks after the initial acute illness. Spirometry testing will be repeated (if subject already had this test at screening) upon their return. Acute respiratory illness includes acute respiratory infection, or other acute illness impacting normal breathing.

Withdrawal of Subjects

The study may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or for other reasons given by the ethics committee concerned.

If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and the Research Ethics Committee will be informed within 15 days of the early termination of the study.

The Investigator will advise the Sponsor of the withdrawal of any subject. Withdrawn subjects will be replaced.

A subject may be withdrawn in any of the following circumstances:

- Adverse events;
- Inter-current illness;
- Protocol violations;
- Withdrawal of consent;
- Termination of the study by the Investigator or Sponsor.

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations, cure, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible and an assessment will be made by the clinical team as to whether follow-up is necessary (i.e. in case of any adverse events).

Expected Duration

The expected duration of the trial is no more than 9 months. The start will be defined as the first patient on their first visit. The end of the study will be defined as the database lock date following the last patient's last visit.

Appendix E-2: Full Study Table

Assessment	Screening	All Study Days (4)								
Time (mins)		Pre-testing (on each study day)	Cont-inuous (automatic recording)	-3	0	3	8	15	30	60
Informed consent	x									
Pregnancy Status/Test	x	x								
Demographics, Medical History & BMI	x									
Concomitant medication check	x	x								
Eligibility Assessment	x	x								
Adverse Events Check		x		x	x	x	x	x	x	x
Breathalyser for alcohol		x								
Drug screen for additional drugs		x								
Spirometry	x									
Vital signs: HR, BP	x	x	x							
Diamorphine administration					x					
Airflow & $ETCO_2$%				x	x	x	x	x	x	x
EMG_{para}			x							
$TcCO_2$			x							
SpO_2%	x	x	x							
Pupil size		x		x	x	x	x	x	x	x
Subjective Drug Effects				x	x	x	x	x	x	x
Staff rating				x	x	x	x	x	x	x

Appendix E-3 Selection of AOO Approval Documents.

NB: Further documentation is available on request.

NHS
Health Research Authority

London - South East Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7109
Fax:0161 625 7919

26 October 2016

Professor Sir John Strang
Addiction Sciences Building
4 Windsor Walk
Denmark Hill
SE5 8BB

Dear Professor Sir Strang

Study Title:	**Acute Opioid Overdose: Improving understanding through a Phase IV Physiological Study**
REC reference:	**16/LO/1765**
Protocol number:	**AOO**
EudraCT number:	**2016-001877-34**
IRAS project ID:	**172751**

The Research Ethics Committee reviewed the above application at the meeting held on 12 October 2016. Thank you for attending to discuss the application.

Provisional opinion

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to Chair, together with Professor Anthony Fox and Professor Zahur Zaman.

Further information or clarification required

1) Please provide written justification for the £100 voucher as this is tradable as monitory value which may introduce enticement to participate in the study.
2) Please amend the Participant Information Sheets:
   a) To clearly state all known risks of taking part in the study.
   b) After the heading 'Do I have to take part?' begin the sentence with 'no'.
3) Please submit the Independent Scientific review for the study.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact Margaret Hutchinson at margaret.hutchinson2@nhs.net.

When submitting a response to the Committee, the requested information should be electronically submitted from IRAS. A step-by-step guide on submitting your response to the REC provisional opinion is available on the HRA website using the following link: http://www.hra.nhs.uk/nhs-research-ethics-committee-rec-submitting-response-provisional-opinion/

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 25 November 2016.

Summary of the discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee discussed the fact that on the street there was an enormous variability of strength on pureness of heroin. As this study was only going to investigate a small dose range of diamorphine, the Committee asked the researchers to explain how the dose range could be increased to replicate the street doses without introducing too great an additional risk.

The researchers explained that this was quite right, and indeed a dilemma the research team faced as it was all about keeping the balance. However for this study the team wanted to determine the signal relevant to respiratory depression and the only way to achieve this was to stress the system enough to get the results. There would be a stepwise approach increasing the dose from 10-20% amplifying the signal. This was an increase the team felt was comfortable. Once this had been explored the team could think about investigating the increase to 40%, but that would be a separate study.

The Committee accepted the response agreed that the risks were tolerable and this study may produce some pilot data which could be built on in the future.

Recruitment arrangements and access to health information, and fair participant selection

The Committee raised a concern around the possible potential for coercion in the recruitment process. There were patients that would be on the diamorphine programme, but not voluntarily so, as it may be a condition of probation. Such patients often have a very chaotic lifestyle. Getting onto steady treatment programme was very difficult for some, and it may not take a great deal for some to lapse back into street heroin. They would require their report to state they had complied with the programme. The concern was that the researchers may appear to be a figure of authority, and by not participating in the study potential participants may be worried that this would affect their report. They may be worried that this may be viewed as having not fully complied, and therefore agree to take part because they felt they had no choice.

The researchers explained that it was very important for people who were in that situation not to be included in the study. If there was that degree of instability then they would be excluded from taking part in the research. That said it was unlikely that all participants would have complete stability, but would have long term involvement with treatment services.

The Committee asked for clarification of how many patients in treatment services would under probation services.

The researchers explained that it would be approximately 25%, however the number of patients in treatment services having had dealings with the law for criminal offences was significantly higher than this.

The Committee advised that the persons taking informed consent would take this into consideration, as to ensure the patients under probation services were not recruited in the study.

The researchers agreed on the importance of this and assured the Committee the persons taking consent would be very experienced members of the clinical team as this patient population was only looked after by very experienced professionals.

The Committee were satisfied with the response.

After the researchers had left the meeting, the Committee raised a concern regarding the £100 voucher that participants would receive. Although the voucher would be awarded in staged payments, the Committee requested written justification for this as they could be sold for cash .This could provide incentive some participants to partake for that reason alone.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee discussed the additional risks of taking an increased dose of diamorphine, which primarily was suffering respiratory arrest.
The Committee were concerned that the risks of taking an increased dose of diamorphine had not been properly explained in the Information Sheet. The Committee acknowledged that participants who had previously been addicted to street heroin which would have been cut and diluted with very poisonous chemicals may well not be overly concerned with the additional risk for the increased dose of the pharmalogical compound; nonetheless it should be made very clear.
The Committee also stated It should also be made clear that there would be no direct benefit to participants and asked the researchers to explain why this information was missing from the Information Sheet and IRAS Form.

The researchers agreed that this was a very important point and explained that this was a conversation that would be had with participants at the point of recruitment. In terms of the documentation there was no intention to withhold this information and this would be addressed to ensure all the risks were adequately covered within the written information.

The Committee were satisfied with the response and requested the changes be made and the Information Sheet resubmitted for review.

Independent review

The Committee asked why there had been no scientific review conducted for the study.

The researchers explained this had been conducted and had been omitted in error from the submission. This would be submitted to the Committee for review.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper [AOO Cover Letter]	1	26 August 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [KCL Insurances 2016-2017 -single PDF]	1	07 June 2016
GP/consultant information sheets or letters [lettertoGP-clinicianAOO_V1.0]	1.0	18 July 2016
IRAS Checklist XML [Checklist_07102016]		07 October 2016
Letter from sponsor [Sponsor Letter (email) AOO Study]	1	30 September 2016
Participant consent form [ConsentFormAOO_V1.0]	1.0	25 August 2016
Participant information sheet (PIS) [PatientInformationSheetAOO_V1.0]	1.0	14 August 2016
REC Application Form [REC_Form_07102016]		07 October 2016
Research protocol or project proposal [AOOPhaseIVStudyProtocol_V1.1]	1.1	26 August 2016
Summary CV for Chief Investigator (CI) [Summary CV for CI]		
Summary CV for student [Ms Basak Tas]		
Summary CV for supervisor (student research) [Dr James Bell]		
Summary CV for supervisor (student research) [Dr C Jolley]		
Summary of product characteristics (SmPC) [Diamorphine Injection BP 500mg]		14 July 2016

Summary of product characteristics (SmPC) [Diamorphine Injection BP 100mg]		14 July 2016

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

16/LO/1765	**Please quote this number on all correspondence**

Yours sincerely

M. Hutchinson

pp
Professor David Caplin
Chair

Email: nrescommittee.london-southeast@nhs.net

Enclosures:	*List of names and professions of members who were present at the meeting and those who submitted written comments.*
Copy to:	*Ms Helen Critchley* *Ms Jennifer Liebscher, South London and Maudsley NHS Foundation Trust*

Health Research Authority
London - South East Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

25 November 2016

Prof Sir John Strang
Addiction Sciences Building
4 Windsor Walk
Denmark Hill
SE5 8BB

Dear Prof Sir Strang

Study title:	**Acute Opioid Overdose: Improving understanding through a Phase IV Physiological Study**
REC reference:	**16/LO/1765**
Protocol number:	**AOO**
EudraCT number:	**2016-001877-34**
IRAS project ID:	**172751**

Thank you for your letter of , responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair David Caplin and Committee Members Anthony Fox and Zahur Zaman.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager Margaret Hutchinson, nrescommittee.london-southeast@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites listed in the application, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [AOO Cover Letter]	1	26 August 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [KCL Insurances 2016-2017 -single PDF]	1	07 June 2016
GP/consultant information sheets or letters [lettertoGP-clinicianAOO_V1.0]	1.0	18 July 2016
IRAS Checklist XML [Checklist_07102016]		07 October 2016
IRAS Checklist XML [Checklist_09112016]		09 November 2016
Letter from sponsor [Sponsor Letter (email) AOO Study]	1	30 September 2016
Other [References for Response Letter]	1.0	08 November 2016
Other [HRA guidance on Payments and Incentives]	1.0	21 April 2014
Other [Response Letter to REC]	1.0	08 November 2016
Participant consent form [ConsentFormAOO_V1.0]	1.0	25 August 2016
Participant information sheet (PIS) [PatientInformationSheetAOO_V1.1]	1.1	31 October 2016
REC Application Form [REC_Form_07102016]		07 October 2016

Referee's report or other scientific critique report [AOOStudy-ScientificReview-JMarsden]	1.0	30 November 2015
Research protocol or project proposal [AOOPhaseIVStudyProtocol_V1.1]	1.1	26 August 2016
Summary CV for Chief Investigator (CI) [Summary CV for CI]		
Summary CV for student [Ms Basak Tas]		
Summary CV for supervisor (student research) [Dr James Bell]		
Summary CV for supervisor (student research) [Dr C Jolley]		
Summary of product characteristics (SmPC) [Diamorphine Injection BP 500mg]		14 July 2016
Summary of product characteristics (SmPC) [Diamorphine Injection BP 100mg]		14 July 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

Professor David Caplin
Chair

Email:nrescommittee.london-southeast@nhs.net

Enclosures:	"After ethical review – guidance for researchers" *[SL-AR1]*
Copy to:	*Ms Helen Critchley* *Ms Jennifer Liebscher, South London and Maudsley NHS Foundation Trust*

Prof Sir John Strang
Addiction Sciences Building
4 Windsor Walk
Denmark Hill
SE5 8BB

Email: hra.approval@nhs.net

19 January 2017

Dear Professor Strang,

Letter of HRA Approval

Study title:	**Acute Opioid Overdose: Improving understanding through a Phase IV Physiological Study**
IRAS project ID:	**172751**
EudraCT number:	**2016-001877-34**
Protocol number:	**AOO**
REC reference:	**16/LO/1765**
Sponsor	**King's College London**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

Health Research Authority

London - South East Research Ethics Committee

Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

<u>Please note: This is the favourable opinion of the REC only and does not allow</u> the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

13 July 2017

Basak Tas
Addictions Department
Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
King's College London
Addiction Sciences Building
Room B1.08
4 Windsor Walk
London
SE5 8BB

Dear Ms Tas

Study title:	**Acute Opioid Overdose: Improving understanding through a Phase IV Physiological Study**
REC reference:	**16/LO/1765**
Protocol number:	**AOO**
EudraCT number:	**2016-001877-34**
Amendment number:	**Substantial Amendment 1**
Amendment date:	**08 June 2017**
IRAS project ID:	**172751**

The above amendment was reviewed by the Sub-Committee held by correspondence.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The members of the Sub-Committee raised no ethical concerns regarding this amendment and were content to issue a Favourable Opinion.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper		21 June 2017
Notice of Substantial Amendment (CTIMP)	Substantial Amendment 1	08 June 2017
Participant information sheet (PIS) [tracked]	1.2	15 May 2017
Research protocol or project proposal [tracked]	1.3	02 June 2017
Research protocol or project proposal [clean]	1.3	02 June 2017

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

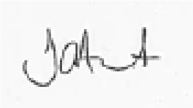
Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/



pp
Professor David Caplin
Chair

E-mail: nrescommittee.london-southeast@nhs.net

Enclosures:	*List of names and professions of members who took part in the review*
Copy to:	*Ms Jennifer Liebscher, South London and Maudsley NHS Foundation Trust* *Prof Sir John Strang* *Ms Helen Critchley*

MHRA
151 Buckingham Palace Road
London SW1W 9SZ
United Kingdom

mhra.gov.uk

Ms H Critchley
KINGS COLLEGE LONDON AND SOUTH LONDON AND MAUDSLEY NHS FOUNDATION TRUST
KING'S HEALTH PARTNERS CLINICAL TRIALS OFFICE
FLOOR 16, TOWER WING, GREAT MAZE POND
LONDON
SE1 9RT
UNITED KINGDOM

04/08/2017

Dear Ms H Critchley

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	21462/0203/001-0002
Eudract Number:	2016-001877-34
Product:	Diamorphine Hydrochloride BP
Protocol number:	AOO
Substantial Amendment Code Number:	Protocol version 1.3, dated 02 June 2017

NOTICE OF ACCEPTANCE OF AMENDMENT

I am writing to inform you that the Licensing Authority accepts the proposed amendment to your clinical trial authorisation (CTA), received on 12/07/2017.

This amendment may therefore be made.

You are reminded that where it is appropriate, the Ethics Committee should also be notified of amendments.

Yours sincerely,

Clinical Trials Unit
MHRA

NHS
Health Research Authority

London - South East Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

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13 July 2017

Basak Tas
Addictions Department
Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
King's College London
Addiction Sciences Building
Room B1.08
4 Windsor Walk
London
SE5 8BB

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Study title:	**Acute Opioid Overdose: Improving understanding through a Phase IV Physiological Study**
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Approved documents

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Statement of compliance

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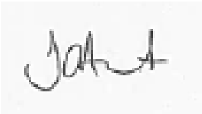

pp
Professor David Caplin
Chair

E-mail: nrescommittee.london-southeast@nhs.net

Enclosures:	*List of names and professions of members who took part in the review*
Copy to:	*Ms Jennifer Liebscher, South London and Maudsley NHS Foundation Trust* *Prof Sir John Strang* *Ms Helen Critchley*

AOO Study - Sponsor green light for recruitment

Englander, Sophie

Mon 04/12/2017 14:03

To: Strang, John <john.strang@kcl.ac.uk>; Tas, Basak <basak.tas@kcl.ac.uk>;

Cc: KHP: SLaM: Ivin, Glynis <Glynis.Ivin@slam.nhs.uk>; KHP: SLaM: Heasman, Martin <Martin.Heasman@slam.nhs.uk>; Brumarescu, Ingrid <ingrid.brumarescu@kcl.ac.uk>;

Dear Professor Strang and Basak,

I am delighted to give sponsor green light for the AOO trial to start recruiting at SLaM. If you have not done so already, you will need to confirm that IMP has been received in pharmacy and that they are happy for the trial to go live.

As discussed, I will perform the first monitoring visit as soon as possible after the first patient has been recruited, so please keep me informed.

I wish you every success with the trial and please do not hesitate to contact me if I can be of any assistance.

Kind regards

Sophie Englander
Clinical Research Associate
King's Health Partners Clinical Trials Office
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Floor 16 Tower Wing | Guy's Hospital | Great Maze Pond | SE1 9RT
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Health Research Authority

London - South East Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

03 May 2018

Ms Basak Tas
Addiction Sciences Building
4 Windsor Walk
Denmark Hill
SE5 8BB

Dear Ms Tas

Study title:	**Acute Opioid Overdose: Improving understanding through a Phase IV Physiological Study**
REC reference:	**16/LO/1765**
Protocol number:	**AOO**
EudraCT number:	**2016-001877-34**
Amendment number:	**Substantial Amendment 2**
Amendment date:	**20 April 2018**
IRAS project ID:	**172751**

This amendment consisted of an update to the Protocol and PISICF as intravenous use is likely to be a problem for several of the patients who are otherwise suitable study subjects. It is not appropriate to enter veins that the participant is uncomfortable with or is more at risk of complications with. Consequently, for patients for whom IV use cannot be achieved, it is proposed to administer the injection of heroin intramuscularly (instead of intravenously), and administer any rescue injection of naloxone by intramuscular (instead of intravenous) injection. Intramuscular route is still an approved route of administration for the rescue medication naloxone and for adrenaline if they are needed.

The above amendment was reviewed by the Sub-Committee held by correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The members of the Sub-Committee raised no ethical concerns regarding this amendment and were content to issue a Favourable opinion.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper		20 April 2018
Notice of Substantial Amendment (CTIMP)	Substantial Amendment 2	20 April 2018
Participant information sheet (PIS) [tracked]	1.3	22 March 2018
Research protocol or project proposal [tracked]	1.4	07 March 2018

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

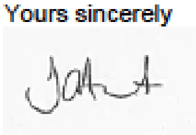
This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

Yours sincerely



pp
Ms Stephanie Cooper
Chair

E-mail: nrescommittee.london-southeast@nhs.net

Enclosures:	*List of names and professions of members who took part in the review*
Copy to:	*Ms Jennifer Liebscher, South London and Maudsley NHS Foundation Trust* *Ms Basak Tas*

Appendix F. Outputs During PhD

Presentations during PhD

2018:

MRC Addictions Research Summer Meeting **|** *June, London, UK*

Oral Presentation: "Heroin Overdose: Experimental Testing and Measurement in the Laboratory: Preliminary Findings."

'Heroin On Trial': Heroin-Assisted Treatment in the UK **|** *May, London, UK*

Oral presentation: "Deaths whilst on pharmaceutical heroin: look-back on the 'Old British System"

2017:

Society for the Study of Addictions Symposium **|** *November, Newcastle, UK*

Poster Presentation: "An Observational Study of the Severity of Respiratory Depression in Chronic Opioid Dependence."

27th International Congress of the European Respiratory Society **|** *September, Milan, Italy*

Poster Presentation: "An Observational Study of the Severity of Respiratory Depression (R_{DP}) in Opioid Dependent Patients (ODP)."

2nd Lisbon Addictions Conference **|** *October, Lisbon, Portugal*

Oral presentation: "An Observational Study of the Severity of Respiratory Depression in Chronic Opioid Dependence."

2016:

Institute of Psychiatry, Psychology & Neuroscience PhD Symposium **|** *May, London, UK*

Poster Presentation: "Pharmaceutical Heroin Prescribing and Mortality Rates: The 'British System' of the 1960s and Early 1970s."

2015:

Society for the Study of Addictions Symposium **|** *October, York, UK*

Poster Presentation: “Pharmaceutical Heroin Prescribing and Mortality Rates: The ‘British System’ of the 1960s and Early 1970s.”

1st Lisbon Addictions Conference **|** *September, Lisbon, Portugal*

Oral presentation: “Pharmaceutical Heroin Prescribing and Mortality Rates: The ‘British System’ of the 1960s and Early 1970s.”

Publications during PhD

1. **Tas, B**. & McDonald, R (2016). Commentary on Darke & Duflou (2016): Heroin-related deaths – identifying a window for intervention. *Addiction* 111(9):1614-1615.

2. **Tas, B.** & Day, E. (2016). Pharmacology and physiological mechanisms of opioid overdose and reversal. In: Strang, J. & McDonald, R. (Eds) (2016). Preventing opioid overdose deaths with take-home naloxone. *EMCDDA Insights*. Lisbon, Portugal.

3. Strang, J., McDonald, R., **Tas, B.** & Day, E (2016). Clinical provision of nasal naloxone without prior experimental testing and without regulatory approval – imaginative shortcut or dangerous bypass of essential safety procedures? *Addiction* 111(4) doi:10.1111/add.13209.

4. Winston, I., McDonald, R., Tas, B. & Strang, J. (2015). Heroin Overdose Resuscitation with Naloxone: Patient Uses Own Prescribed Supply to Save the Life of a Peer. BMJ Case Reports doi:10.1136/bcr-2015-210391